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PCT

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US98/00617 (22) International Filing Date: 13 January 1998 (13.01.98) (30) Priority Data: 60/035,614 17 January 1997 (17.01.97) US 9702788.2 11 February 1997 (11.02.97) GB 60/062,594 20 October 1997 (20.10.97) US 9725996.4 9 December 1997 (09.12.97) GB (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): DUGGAN, Mark, E. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: INTEGRIN ANTAGONISTS (57) Abstract <p>This invention relates to certain novel compounds and derivatives thereof, their synthesis, and their use as vitronectin receptor antagonists. The vitronectin receptor antagonist compounds of the present invention are $\alpha v\beta 3$ antagonists, $\alpha v\beta 5$ antagonists or dual $\alpha v\beta 3/\alpha v\beta 5$ antagonists useful for inhibiting bone resorption, treating and preventing osteoporosis, and inhibiting restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation, viral disease, and tumor growth.</p> <p>9/916,977</p> <p>tetraphosphoryl</p>			

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TITLE OF THE INVENTION

INTEGRIN ANTAGONISTS

FIELD OF THE INVENTION

5 The present invention is related to U.S. provisional applications Serial Nos. 60/035,614, filed January 17, 1997, and 60/062,594, filed October 20, 1997, the contents of which are hereby incorporated by reference.

10 The present invention provides novel compounds and derivatives thereof, their synthesis, and their use as vitronectin receptor ligands. More particularly, the compounds of the present invention are $\alpha v \beta 3$ antagonists, $\alpha v \beta 5$ antagonists or dual $\alpha v \beta 3 / \alpha v \beta 5$ antagonists useful for inhibiting bone resorption, treating and preventing osteoporosis, and inhibiting vascular restenosis, diabetic retinopathy, 15 macular degeneration, angiogenesis, atherosclerosis, inflammation, viral disease, and tumor growth.

BACKGROUND OF THE INVENTION

20 This invention relates to compounds for inhibiting bone resorption that is mediated by the action of a class of cells known as osteoclasts.

 Osteoclasts are multinucleated cells of up to 400 μm in diameter that resorb mineralized tissue, chiefly calcium carbonate and calcium phosphate, in vertebrates. They are actively motile cells that 25 migrate along the surface of bone. They can bind to bone, secrete necessary acids and proteases and thereby cause the actual resorption of mineralized tissue from the bone.

 More specifically, osteoclasts are believed to exist in at least two physiological states. In the secretory state, osteoclasts are flat, 30 attach to the bone matrix via a tight attachment zone (sealing zone), become highly polarized, form a ruffled border, and secrete lysosomal enzymes and protons to resorb bone. The adhesion of osteoclasts to bone surfaces is an important initial step in bone resorption. In the migratory or motile state, the osteoclasts migrate across bone matrix 35 and do not take part in resorption until they attach again to bone.

Integrins are transmembrane, heterodimeric, glycoproteins which interact with extracellular matrix and are involved in osteoclast attachment, activation and migration. The most abundant integrin in osteoclasts (rat, chicken, mouse and human) is the vitronectin receptor, or $\alpha v \beta 3$, thought to interact in bone with matrix proteins that contain the RGD sequence. Antibodies to $\alpha v \beta 3$ block bone resorption in vitro indicating that this integrin plays a key role in the resorptive process. There is increasing evidence to suggest that $\alpha v \beta 3$ ligands can be used effectively to inhibit osteoclast mediated bone resorption in vivo in mammals.

The current major bone diseases of public concern are osteoporosis, hypercalcemia of malignancy, osteopenia due to bone metastases, periodontal disease, hyperparathyroidism, periarticular erosions in rheumatoid arthritis, Paget's disease, immobilization-induced osteopenia, and glucocorticoid treatment.

All these conditions are characterized by bone loss, resulting from an imbalance between bone resorption (breakdown) and bone formation, which continues throughout life at the rate of about 14% per year on the average. However, the rate of bone turnover differs from site to site, for example, it is higher in the trabecular bone of the vertebrae and the alveolar bone in the jaws than in the cortices of the long bones. The potential for bone loss is directly related to turnover and can amount to over 5% per year in vertebrae immediately following menopause, a condition which leads to increased fracture risk.

There are currently 20 million people with detectable fractures of the vertebrae due to osteoporosis in the United States. In addition, there are 250,000 hip fractures per year attributed to osteoporosis. This clinical situation is associated with a 12% mortality rate within the first two years, while 30% of the patients require nursing home care after the fracture.

Individuals suffering from all the conditions listed above would benefit from treatment with agents which inhibit bone resorption.

Additionally, $\alpha v \beta 3$ ligands have been found to be useful in treating and/or inhibiting restenosis (recurrence of stenosis after corrective surgery on the heart valve), atherosclerosis, diabetic

retinopathy, macular degeneration and angiogenesis (formation of new blood vessels), and inhibiting viral disease. Moreover, it has been postulated that the growth of tumors depends on an adequate blood supply, which in turn is dependent on the growth of new vessels into the tumor; thus, inhibition of angiogenesis can cause tumor regression in animal models. (See, Harrison's Principles of Internal Medicine, 12th ed., 1991). $\alpha v\beta 3$ antagonists, which inhibit angiogenesis, are therefore useful in the treatment of cancer for inhibiting tumor growth. (See e.g., Brooks et al., *Cell*, 79:1157-1164 (1994)).

Moreover, compounds of this invention can also inhibit neovascularization by acting as antagonists of the integrin receptor $\alpha v\beta 5$. A monoclonal antibody for $\alpha v\beta 5$ has been shown to inhibit VEGF-induced angiogenesis in rabbit cornea and the chick chorioallantoic membrane model; M.C. Friedlander, et.al., *Science* 270, 1500-1502, 1995. Thus, compounds that antagonize $\alpha v\beta 5$ are useful for treating and preventing macular degeneration, diabetic retinopathy, and tumor growth.

In addition, certain compounds of this invention antagonize both the $\alpha v\beta 3$ and $\alpha v\beta 5$ receptors. These compounds, referred to as "dual $\alpha v\beta 3/\alpha v\beta 5$ antagonists," are useful for inhibiting bone resorption, treating and preventing osteoporosis, and inhibiting vascular restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation and tumor growth.

It is an object of the present invention to identify compounds which bind to the $\alpha v\beta 3$ receptor, $\alpha v\beta 5$ receptor or both the $\alpha v\beta 3$ and $\alpha v\beta 5$ receptors.

It is a further object of the invention to identify compounds which act as antagonists of the $\alpha v\beta 3$ receptor. It is another object of the invention to identify $\alpha v\beta 3$ antagonist compounds which are useful agents for inhibiting: bone resorption mediated by osteoclast cells, restenosis, atherosclerosis, inflammation, diabetic retinopathy, macular degeneration and angiogenesis in animals, preferably mammals, especially humans. Still another object of the invention is to identify $\alpha v\beta 3$ antagonists which cause tumor regression and/or inhibit tumor growth in animals.

A further object of the invention is to identify $\alpha\beta 3$ antagonists useful for preventing or treating osteoporosis. An additional object of the invention is to identify $\alpha\beta 3$ antagonists useful for treating cancer.

5 It has now been found that the compounds of the present invention, $\alpha\beta 3$ ligands, are useful for inhibiting bone resorption in mammals. Thus, the compounds of the present invention are useful for preventing or reducing the incidence of osteoporosis. Additionally, the $\alpha\beta 3$ ligands of the present invention are also useful for treating and/or
 10 inhibiting restenosis, diabetic retinopathy, macular degeneration, viral disease, atherosclerosis and/or angiogenesis in mammals.

SUMMARY OF THE INVENTION

15 The present invention provides $\alpha\beta 3$ antagonist compounds of the formula



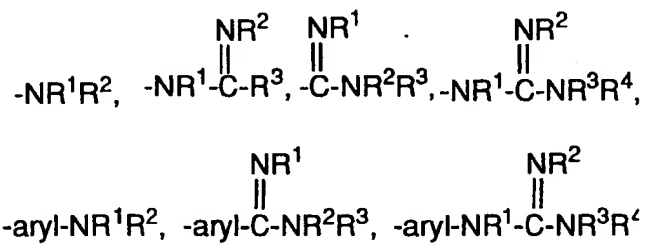
wherein:

20

Aryl is a 6-membered aromatic ring containing 0, 1, 2 or 3 nitrogen atoms and either unsubstituted or substituted with R^8 and R^9 ;

X is selected from

25



a 5- or 6-membered monocyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O or S wherein the 5- or 6-membered ring system is either

unsubstituted or substituted with R¹, R², R³ and R⁴, or

5 a 9- to 14-membered polycyclic ring system, wherein one or more of the rings is aromatic, and wherein the polycyclic ring system contains 0, 1, 2, 3 or 4 heteroatoms selected from N, O or S, and wherein the polycyclic ring system is either unsubstituted or substituted with R¹, R², R³ and R⁴;

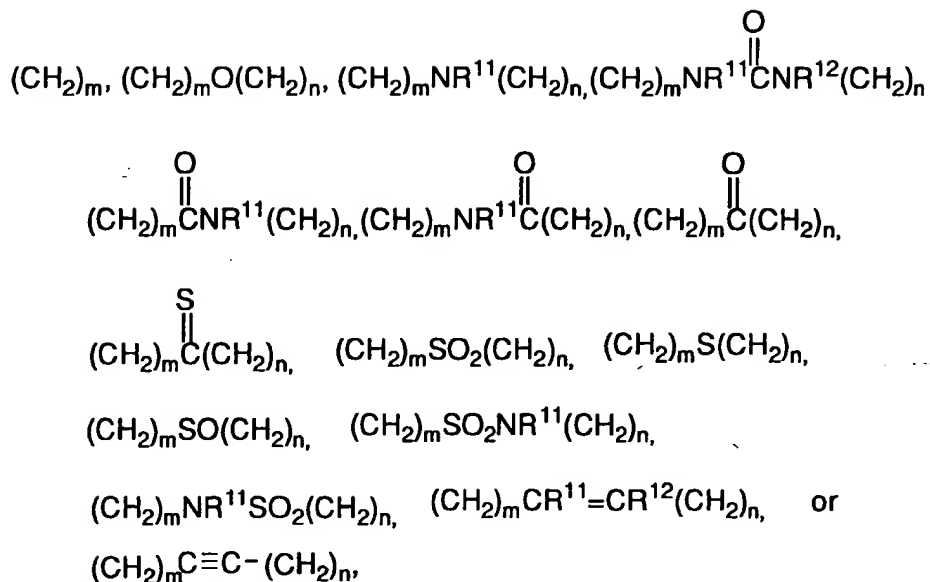
Y is selected from

10 C₀₋₈ alkylene,
 C₃₋₁₀ cycloalkyl,
 C₀₋₈ alkylene-NR¹⁰-CO-C₀₋₈ alkylene,
 C₀₋₈ alkylene-CONR¹⁰-C₀₋₈ alkylene,
 C₀₋₈ alkylene-O-C₀₋₈ alkylene,
 15 C₀₋₈ alkylene-NR¹⁰-C₀₋₈ alkylene,
 C₀₋₈ alkylene-S(O)₀₋₂-C₀₋₈ alkylene,
 C₀₋₈ alkylene-SO₂-NR¹⁰-C₀₋₈ alkylene,
 C₀₋₈ alkylene-NR¹⁰-SO₂-C₀₋₈ alkylene,
 C₀₋₈ alkylene-CO-C₀₋₈ alkylene,
 20 (CH₂)₀₋₆ aryl(CH₂)₀₋₆,
 (CH₂)₀₋₆ aryl-CO-(CH₂)₀₋₆,
 (CH₂)₀₋₆ aryl-CO-NR¹⁰-(CH₂)₀₋₆,
 (CH₂)₀₋₆ arylNR¹⁰CO(CH₂)₀₋₆, or

$$\begin{array}{c} \text{OR}^1 \\ | \\ (\text{CH}_2)_{0-8}\text{CH}(\text{CH}_2)_{0-8}; \end{array}$$

25

Z and A are each independently selected from



where m and n are each independently an integer from 0 to 6;

B is



where p is an integer from 1 to 3;

R¹, R², R³, R⁴, R⁵, R⁸, R⁹, R¹⁰, R¹¹ and R¹² are each independently selected from

- 10 hydrogen,
 halogen,
 C₁₋₁₀ alkyl,
 aryl C₀₋₈ alkyl,
 amino C₀₋₈ alkyl,
 15 C₁₋₃ acylamino C₀₋₈ alkyl,
 C₁₋₆ alkylamino C₀₋₈ alkyl,

5 C₁₋₆ dialkylamino C₀₋₈ alkyl,
aryl C₀₋₆ alkylamino C₀₋₆ alkyl,
C₁₋₄ alkoxyamino C₀₋₈ alkyl,
hydroxy C₁₋₆ alkylamino C₀₋₈ alkyl,
C₁₋₄ alkoxy C₀₋₆ alkyl,
hydroxycarbonyl C₀₋₆ alkyl,
C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl,
hydroxycarbonyl C₀₋₆ alkyloxy,
hydroxy C₁₋₆ alkylamino C₀₋₆ alkyl or
10 hydroxy C₀₋₆ alkyl;

R⁶ is selected from
hydrogen,
fluorine,
15 C₁₋₈ alkyl,
hydroxyl,
hydroxy C₁₋₆ alkyl,
carboxy C₀₋₆ alkyl,
C₁₋₆ alkyloxy,
20 C₁₋₆ alkylcarbonyl,
aryl C₀₋₆ alkylcarbonyl,
C₁₋₆ alkylcarbonyloxy,
aryl C₀₋₆ alkylcarbonyloxy,
C₁₋₆ alkylaminocarbonyloxy,
25 C₃₋₈ cycloalkyl,
aryl C₀₋₆ alkyl,
C₀₋₆ alkylamino C₀₋₆ alkyl,
C₀₋₆ dialkylamino C₀₋₆ alkyl,
C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl,
30 aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl,
C₁₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
aryl C₀₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,
aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,

5 C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
aryl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
10 C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,
aryl C₀₋₆ alkylsulfonyl C₀₋₆ alkyl,
C₁₋₆ alkylcarbonyl C₀₋₆ alkyl,
aryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl,
C₁₋₆ alkylthiocarbonylamino C₀₋₆ alkyl, or
15 aryl C₀₋₆ alkylthiocarbonylamino C₀₋₆ alkyl;
wherein the alkyl or N atoms may be unsubstituted or
substituted with R⁵;

R⁷ is selected from
15 C₇₋₂₀ polycyclyl C₀₋₈ alkylsulfonylamino C₀₋₆ alkyl;
C₇₋₂₀ polycyclyl C₀₋₈ alkylcarbonylamino C₀₋₆ alkyl;
C₇₋₂₀ polycyclyl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl;
C₇₋₂₀ polycyclyl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl or
C₇₋₂₀ polycyclyl C₀₋₈ alkyloxycarbonylamino C₀₋₆ alkyl;
20 wherein the polycyclyl may be unsubstituted or substituted with
R¹⁴, R¹⁵, R¹⁶ and R¹⁷; and wherein any of the alkyl groups may
be unsubstituted or substituted with R¹⁴ and R¹⁵;

R¹³ is selected from
25 hydroxy,
C₁₋₈ alkyloxy,
aryl C₀₋₆ alkyloxy,
C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy,
aryl C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy,
30 C₁₋₆ dialkylaminocarbonylmethyloxy,
aryl C₁₋₆ dialkylaminocarbonylmethyloxy or
an L- or D-amino acid joined by an amide linkage and
wherein the carboxylic acid moiety of said amino acid
is as the free acid or is esterified by C₁₋₆ alkyl; and

R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are each independently selected from
hydrogen, halogen, C₁₋₁₀ alkyl, C₃₋₈ cycloalkyl, oxo, aryl,
aryl C₁₋₈ alkyl, amino, amino C₁₋₈ alkyl, C₁₋₃ acylamino,
5 C₁₋₃ acylamino C₁₋₈ alkyl, C₁₋₆ alkylamino, C₁₋₆ alkylamino-
C₁₋₈ alkyl, C₁₋₆ dialkylamino, C₁₋₆ dialkylamino C₁₋₈ alkyl,
C₁₋₄ alkoxy, C₁₋₄ alkoxy C₁₋₆ alkyl, hydroxycarbonyl,
hydroxycarbonyl C₁₋₆ alkyl, C₁₋₃ alkoxycarbonyl,
C₁₋₃ alkoxycarbonyl C₁₋₆ alkyl, hydroxycarbonyl-
10 C₁₋₆ alkyloxy, hydroxy, hydroxy C₁₋₆ alkyl, C₁₋₆ alkyloxy-
C₁₋₆ alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy,
trifluoroethoxy, C₁₋₈ alkyl-S(O)_q, C₁₋₈ alkylaminocarbonyl,
C₁₋₈ dialkylaminocarbonyl, C₁₋₈ alkyloxycarbonylamino,
C₁₋₈ alkylaminocarbonyloxy or C₁₋₈ alkylsulfonylamino;

15

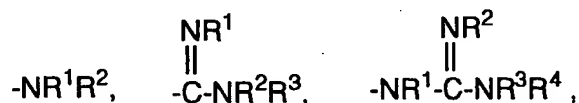
and the pharmaceutically acceptable salts thereof;

provided that the compound is not 4-[2-(1,2,3,4-Tetrahydro-1,8-
naphthyridin-7-yl)ethyl]benzoyl-2(S)[1(S)10-camphorsulfonylamino] β-
alanine ethyl ester (1-14) or 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-
20 yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamino] β-alanine (1-15).

In one embodiment of the invention is the compound
wherein

25 Aryl is a 6-membered aromatic ring containing 0, 1 or 2 nitrogen atoms
wherein Aryl is unsubstituted or substituted with R⁸ and R⁹;

X is selected from



30 a 5- or 6-membered monocyclic aromatic or nonaromatic ring
system containing 0, 1 or 2 heteroatoms selected from N, O
or S wherein the 5- or 6-membered ring system is either

unsubstituted or substituted with R^1 and R^2 , or

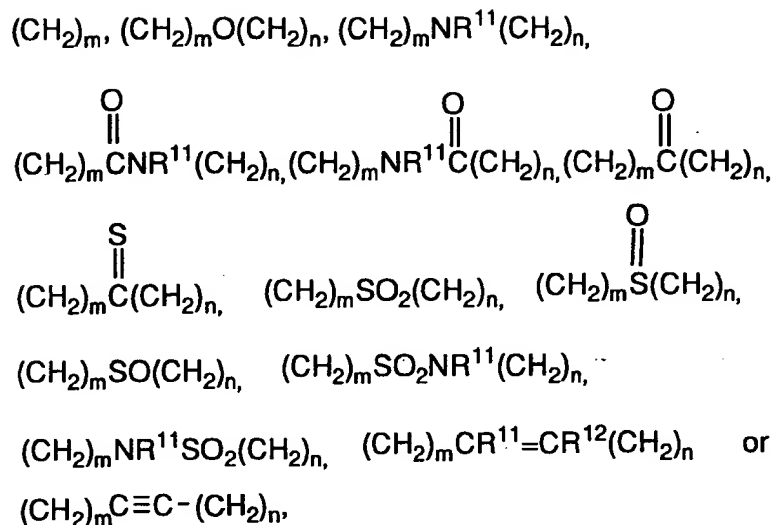
5 a 9- to 14-membered fused polycyclic ring system, wherein one or more of the rings is aromatic, and wherein the polycyclic ring system contains 0, 1, 2 or 3 heteroatoms selected from N, O or S, and wherein the polycyclic ring system is either unsubstituted or substituted with R^1 and R^2 ;

Y is selected from the group consisting of

10 C₀₋₈ alkylene,
 C₃₋₁₀ cycloalkyl,
 C₀₋₈ alkylene-NR¹⁰-CO-C₀₋₈ alkylene,
 C₀₋₈ alkylene-CONR¹⁰-C₀₋₈ alkylene,
 C₀₋₈ alkylene-O-C₀₋₈ alkylene,
 15 C₀₋₈ alkylene-NR¹⁰-C₀₋₈ alkylene,
 C₀₋₈ alkylene-S(O)₀₋₂-C₀₋₈ alkylene,
 C₀₋₈ alkylene-SO₂-NR¹⁰-C₀₋₈ alkylene,
 C₀₋₈ alkylene-NR¹⁰-SO₂-C₀₋₈ alkylene,
 C₀₋₈ alkylene-CO-C₀₋₈ alkylene,
 20 (CH₂)₀₋₆ aryl(CH₂)₀₋₆,
 (CH₂)₀₋₆ aryl-CO-(CH₂)₀₋₆,
 (CH₂)₀₋₆ aryl-CO-NH-(CH₂)₀₋₆, or

$$\begin{array}{c} \text{OR}^1 \\ | \\ (\text{CH}_2)_{0-8}\text{CH}(\text{CH}_2)_{0-8} \end{array}$$

Z and A are each independently selected from



where m and n are each independently an integer from 0 to 4;

R¹, R², R³, R⁴, R⁵, R⁸, R⁹, R¹⁰, R¹¹ and R¹² are each independently

5 selected from

hydrogen,

halogen,

C₁₋₁₀ alkyl,

aryl C₀₋₈ alkyl,

10 amino C₀₋₈ alkyl,

C₁₋₃ acylamino C₀₋₈ alkyl,

C₁₋₆ alkylamino C₀₋₈ alkyl,

C₁₋₆ dialkylamino C₀₋₈ alkyl,

aryl C₀₋₆ alkylamino C₀₋₆ alkyl,

15 C₁₋₄ alkoxyamino C₀₋₈ alkyl,

hydroxy C₁₋₆ alkylamino C₀₋₈ alkyl,

C₁₋₄ alkoxy C₀₋₆ alkyl, or

C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl;

20 R⁶ is selected from

hydrogen,

C₁₋₈ alkyl or

aryl C₀₋₆ alkyl;

R⁷ is selected from

C₇₋₁₅ polycyclyl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl or

C₇₋₁₅ polycyclyl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl;

5 wherein the polycyclyl may be unsubstituted or substituted with
R¹⁴, R¹⁵, R¹⁶ and R¹⁷; and wherein any of the alkyl groups may
be unsubstituted or substituted with R¹⁴ and R¹⁵;

and all other variables are as defined above;

10 and the pharmaceutically acceptable salts thereof;

provided that the compound is not 4-[2-(1,2,3,4-Tetrahydro-1,8-
naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamino] β-
alanine ethyl ester (1-14) or 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-
15 yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamino] β-alanine (1-15).

In a class of the invention is the compound

wherein

Aryl is a phenyl or pyridyl ring wherein the phenyl or pyridyl ring is
20 unsubstituted or substituted with R⁸;

X is

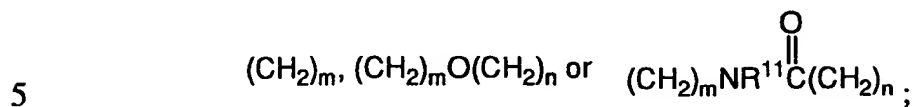
25 a 9- to 14-membered fused polycyclic ring system, wherein one or
more of the rings is aromatic, and wherein the polycyclic ring
system contains 0, 1, 2 or 3 heteroatoms selected from N, O or S,
and wherein the polycyclic ring system is either unsubstituted or
substituted with R¹ and R²;

Y is selected from

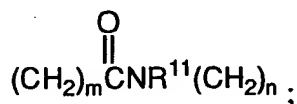
30 C₀₋₆ alkylene,
C₀₋₆ alkylene-NR¹⁰-CO-C₀₋₆ alkylene,
C₀₋₆ alkylene-CONR¹⁰-C₀₋₆ alkylene,
C₀₋₆ alkylene-O-C₀₋₆ alkylene,
C₀₋₆ alkylene-NR¹⁰-C₀₋₆ alkylene,
35 C₀₋₆ alkylene-S(O)₀₋₂-C₀₋₆ alkylene,

C₀₋₆ alkylene-SO₂-NR¹⁰-C₀₋₆ alkylene, or
C₀₋₆ alkylene-aryl-C₀₋₆ alkylene;

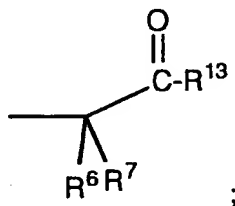
Z is selected from



A is



10 B is



R¹, R², R³, R⁴, R⁵, R⁸, R⁹, R¹⁰, R¹¹ and R¹² are each independently selected from

- 15 hydrogen,
halogen,
C₁₋₁₀ alkyl,
aryl C₀₋₈ alkyl,
C₁₋₄ alkoxy C₀₋₆ alkyl, or
20 C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl;

R⁶ is hydrogen;

R⁷ is selected from

C7-10 polycyclyl C0-6 alkylsulfonylamino C0-6 alkyl or
C7-10 polycyclyl C0-6 alkylcarbonylamino C0-6 alkyl;
wherein the polycyclyl may be unsubstituted or substituted with
R¹⁴, R¹⁵, R¹⁶ and R¹⁷;

5

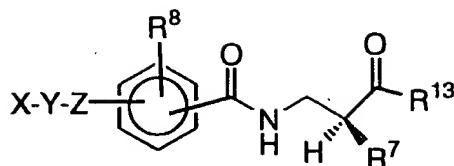
R¹³ is selected from
hydroxy or
C₁₋₈ alkyloxy;

10 R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are each independently selected from
hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, oxo, amino,
amino C₁₋₈ alkyl, C₁₋₃ acylamino, C₁₋₃ acylamino C₁₋₈ alkyl,
C₁₋₆ alkylamino, C₁₋₆ alkylamino C₁₋₈ alkyl,
C₁₋₆ dialkylamino, C₁₋₆ dialkylamino C₁₋₈ alkyl,
15 C₁₋₄ alkoxy, C₁₋₄ alkoxy C₁₋₆ alkyl, hydroxycarbonyl,
hydroxycarbonyl C₁₋₆ alkyl, C₁₋₃ alkoxycarbonyl,
C₁₋₃ alkoxycarbonyl C₁₋₆ alkyl, hydroxycarbonyl-
C₁₋₆ alkyloxy, hydroxy, hydroxy C₁₋₆ alkyl, C₁₋₆ alkyloxy-
C₁₋₆ alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy,
20 trifluoroethoxy, C₁₋₈ alkylsulfonyl, C₁₋₈ alkylaminocarbonyl,
C₁₋₈ alkyloxycarbonylamino, C₁₋₈ alkylaminocarbonyloxy or
C₁₋₈ alkylsulfonylamino;

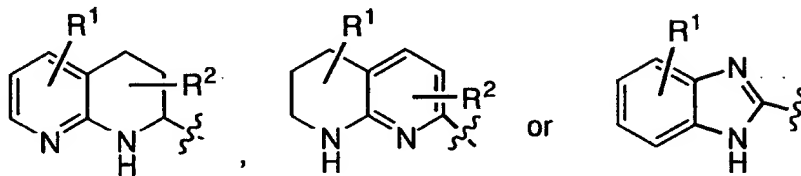
and all other variables are as defined above;
25 and the pharmaceutically acceptable salts thereof;

provided that the compound is not 4-[2-(1,2,3,4-Tetrahydro-1,8-
naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)-10-camphorsulfonylamino] β-
alanine ethyl ester (1-14) or 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-
30 yl)ethyl]benzoyl-2(S)-[1(S)-10-camphorsulfonylamino] β-alanine (1-15).

In a subclass of the invention is the compound of the
formula



wherein X is selected from the group consisting of



Y is selected from

- 5 C0-6 alkylene,
C0-6 alkylene-O-C0-6 alkylene or
C0-6 alkylene-NR¹⁰-C0-6 alkylene;

Z is selected from

- 10 (CH₂)_m or (CH₂)_m-O-(CH₂)_n;

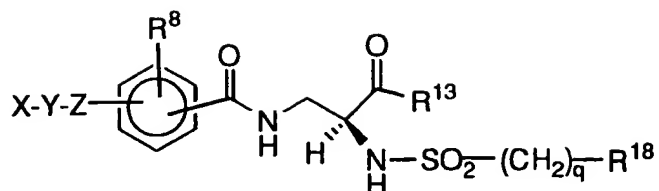
R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are each independently selected from
hydrogen, halogen, C₁-6 alkyl, oxo or hydroxy;

and all other variables are as defined above;

- 15 and the pharmaceutically acceptable salts thereof;

- provided that the compound is not 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamino] β-alanine ethyl ester (1-14) or 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamino] β-alanine (1-15).
- 20

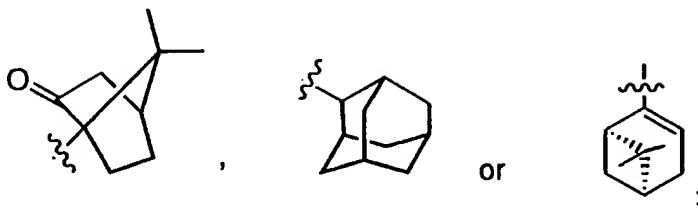
Illustrative of the invention is the compound of the formula:



wherein

q is an integer from 0 to 2;

5 R^{18} is selected from

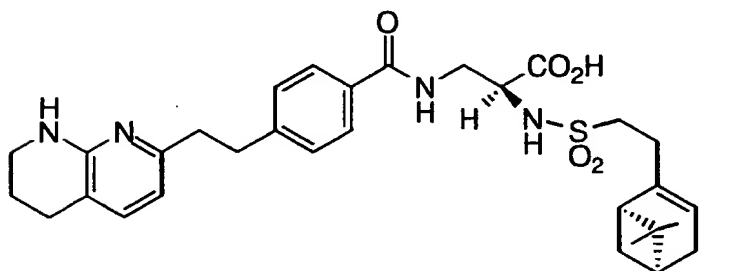
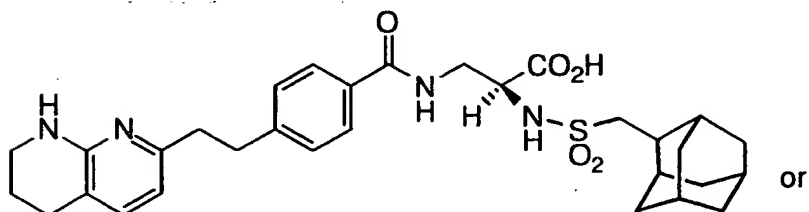
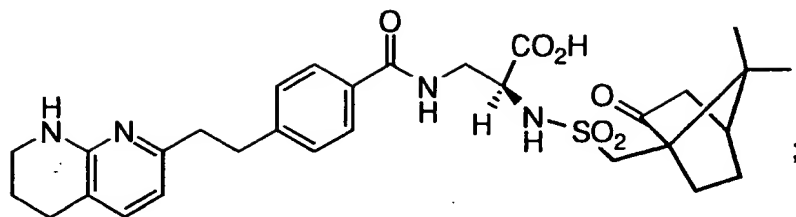


and all other variables are as defined previously;

and the pharmaceutically acceptable salts thereof;

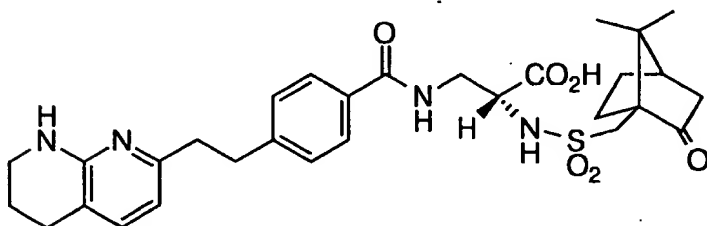
10 provided that the compound is not 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)[1(S)10-camphorsulfonylamino] β -alanine ethyl ester (1-14) or 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamino] β -alanine (1-15).

Exemplifying the invention is the compound selected from



and the pharmaceutically acceptable salts thereof.

An illustration of the invention is the compound of the formula



5

and the pharmaceutically acceptable salts thereof.

Exemplifying the invention is a pharmaceutical composition comprising any of the compounds described above and a

pharmaceutically acceptable carrier. An example of the invention is a pharmaceutical composition made by combining any of the compounds described above and a pharmaceutically acceptable carrier. Another illustration of the invention is a process for making a pharmaceutical composition comprising combining any of the compounds described above and a pharmaceutically acceptable carrier.

Further illustrating the invention is a method of treating and/or preventing a condition mediated by antagonism of a vitronectin receptor in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds described above. Preferably, the condition is selected from bone resorption, osteoporosis, restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammation, viral disease, cancer and tumor growth. More preferably, the condition is selected from osteoporosis and cancer. Most preferably, the condition is osteoporosis.

More specifically exemplifying the invention is a method of eliciting a vitronectin antagonizing effect in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. Preferably, the vitronectin antagonizing effect is an $\alpha v\beta 3$ antagonizing effect; more specifically the $\alpha v\beta 3$ antagonizing effect is selected from inhibition of bone resorption, inhibition of restenosis, inhibition of atherosclerosis, inhibition of angiogenesis, inhibition of diabetic retinopathy, inhibition of macular degeneration, inhibition of inflammation, inhibition of viral disease, or inhibition of tumor growth. Most preferably, the $\alpha v\beta 3$ antagonizing effect is inhibition of bone resorption. Alternatively, the vitronectin antagonizing effect is an $\alpha v\beta 5$ antagonizing effect or a dual $\alpha v\beta 3/\alpha v\beta 5$ antagonizing effect. Examples of $\alpha v\beta 5$ antagonizing effects are inhibition of: restenosis, atherosclerosis, angiogenesis, diabetic retinopathy, macular degeneration, inflammation, or tumor growth. Examples of dual $\alpha v\beta 3/\alpha v\beta 5$ antagonizing effects are inhibition of: bone resorption, restenosis, atherosclerosis, angiogenesis, diabetic

retinopathy, macular degeneration, inflammation, viral disease, or tumor growth.

Additional examples of the invention are methods of inhibiting bone resorption and of treating and/or preventing osteoporosis in a mammal in need thereof, comprising administering to the
5 mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

Additional illustrations of the invention are methods of inhibiting tumor growth and of treating and/or preventing cancer in a
10 mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

More specifically exemplifying the invention is any of the compositions described above, further comprising a therapeutically
15 effective amount of a second bone resorption inhibitor; preferably, the second bone resorption inhibitor is alendronate.

More specifically illustrating the invention is any of the methods of treating and/or preventing osteoporosis and/or of inhibiting bone resorption described above, wherein the compound is administered
20 in combination with a second bone resorption inhibitor; preferably, the second bone resorption inhibitor is alendronate.

Additional illustrations of the invention are methods of treating hypercalcemia of malignancy, osteopenia due to bone metastases, periodontal disease, hyperparathyroidism, periarticular
25 erosions in rheumatoid arthritis, Paget's disease, immobilization-induced osteopenia, and glucocorticoid treatment in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

More particularly exemplifying the invention is the use of any of the compounds described above in the preparation of a medicament for the treatment and/or prevention of osteoporosis in a
30 mammal in need thereof. Still further exemplifying the invention is the use of any of the compounds described above in the preparation of a
35 medicament for the treatment and/or prevention of: bone resorption,

tumor growth, cancer, restenosis, arteriosclerosis, inflammation, viral disease, diabetic retinopathy, macular degeneration and/or angiogenesis.

Another illustration of the invention is a drug which is
5 useful for treating and/or preventing osteoporosis in a mammal in need thereof, the effective ingredient of the said drug being any of the compounds described above. More specifically illustrating the invention is a drug which is useful for treating and/or preventing: bone
10 resorption, tumor growth, cancer, restenosis, arteriosclerosis, inflammation, viral disease, diabetic retinopathy, macular degeneration and/or angiogenesis in a mammal in need thereof, the effective ingredient of the said drug being any of the compounds described above.

Additional illustrations of the invention are methods of
15 treating tumor growth in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a compound described above and one or more agents known to be cytotoxic or antiproliferative, e.g., taxol and doxorubicin. Further illustrative are methods of treating tumor growth wherein the compounds of the
20 present invention are administered in conjunction with radiation therapy.

Further illustrative are methods of inhibiting angiogenesis comprising administering a compound as described above in combination with a VEGF (a vascular endothelial growth factor)
25 inhibitor compound. Such combinations are useful for treating disease states such as macular degeneration, diabetic retinopathy, and cancer.

DETAILED DESCRIPTION OF THE INVENTION

Representative compounds of the present invention are
30 $\alpha v\beta 3$ antagonists which display submicromolar affinity for the human $\alpha v\beta 3$ receptor. Compounds of this invention are therefore useful for treating mammals suffering from a condition caused or mediated by the $\alpha v\beta 3$ receptor, who are in need of such therapy. Pharmacologically effective amounts of the compounds, including pharmaceutically
35 acceptable salts thereof, are administered to the mammal, to inhibit: the

activity of mammalian osteoclasts, restenosis, tumor growth, arteriosclerosis, inflammation, macular degeneration, diabetic retinopathy and angiogenesis.

5 The compounds of the present invention are administered in dosages effective to antagonize the $\alpha\text{v}\beta 3$ receptor where such treatment is needed, as, for example, in the prevention or treatment of osteoporosis or cancer. For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." Other salts may, however, be useful in the preparation of the compounds
10 according to the invention or of their pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following:
15 Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Calcium, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycolylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide,
20 Hydrochloride, Hydroxynaphthoate, Iodide, Isothionate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate, Methylbromide, Methylnitrate, Methylsulfate, Mucate, Napsylate, Nitrate, N-methylglucamine ammonium salt, Oleate, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate,
25 Polygalacturonate, Salicylate, Stearate, Sulfate, Subacetate, Succinate, Tannate, Tartrate, Teoclate, Tosylate, Triethiodide and Valerate. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal
30 salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts.

The compounds of the present invention, may have chiral centers and occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers with all isomeric forms being included
35 in the present invention. Therefore, where a compound is chiral, the

separate enantiomers, substantially free of the other, are included within the scope of the invention; further included are all mixtures of the two enantiomers. Also included within the scope of the invention are polymorphs and hydrates of the compounds of the instant invention.

5 The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" 10 shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, 15 for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

 The term "therapeutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the 20 biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

 The term "bone resorption," as used herein, refers to the process by which osteoclasts degrade bone.

 The term "alkyl" shall mean straight, branched or 25 monocyclic alkanes, alkenes or alkynes of the specified number of carbon atoms. Preferably, the term "alkyl" refers to straight or branched chain alkanes of C₁₋₁₀ carbon atoms, or any number within this range (i.e., methyl, ethyl, 1-propyl, 2-propyl, n-butyl, s-butyl, t-butyl, etc.).

 The term "alkenyl" shall mean straight or branched chain 30 alkenes of two to ten total carbon atoms, or any number within this range.

 The term "alkynyl" shall mean straight or branched chain alkynes of two to ten total carbon atoms, or any number within this range.

The term "cycloalkyl" shall mean cyclic rings of alkanes of three to eight total carbon atoms, or any number within this range (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl).

5 The terms "polycyclic" or "polycyclyl," as used herein, refer to unsubstituted or substituted fused or bridged polycyclic systems containing from 7 to 20 carbon atoms and which can contain one or more degrees of unsaturation. Preferably, the term "polycyclyl" refers to unsubstituted or substituted fused or bridged bi- or tri-cyclic systems containing from 7-15 carbon atoms and which can contain one or two
10 degrees of unsaturation. More preferably, the term "polycyclyl" refers to unsubstituted or substituted fused or bridged bi- or tri-cyclic systems containing from 7-10 carbon atoms and which can contain one or two degrees of unsaturation. Examples of preferred polycyclyl systems include, but are not limited to, decaline, camphor, adamantyl
15 and norbornyl.

The term "cycloheteroalkyl," as used herein, shall mean a 3- to 8-membered fully saturated heterocyclic ring containing one or two heteroatoms chosen from N, O, or S. Examples of cycloheteroalkyl groups include, but are not limited to piperidinyl, pyrrolidinyl,
20 azetidiny, morpholinyl, piperazinyl.

The term "alkoxy," as used herein, refers to straight or branched chain alkoxides of the number of carbon atoms specified (e.g., C1-5 alkoxy), or any number within this range (i.e., methoxy, ethoxy, etc.).

25 The term "alkylene" shall include both straight and branched chain alkylenes (e.g., -CH₂-, -CH(CH₃)-, -CH(CH₃)-CH₂-, etc.).

The term "aryl," as used herein, refers to a monocyclic or polycyclic system composed of 5- and 6-membered rings, such that the system comprises at least one fully unsaturated (i.e., aromatic) ring,
30 wherein the rings contain 0, 1, 2, 3 or 4 heteroatoms chosen from N, O or S, and either unsubstituted or substituted with one or more groups independently selected from hydrogen, halogen, C1-10 alkyl, C3-8 cycloalkyl, aryl, aryl C1-8 alkyl, amino, amino C1-8 alkyl, C1-3 acylamino, C1-3 acylamino C1-8 alkyl, C1-6 alkylamino, C1-6 alkylamino
35 C1-8 alkyl, C1-6 dialkylamino, C1-6 dialkylamino-C1-8 alkyl, C1-4 alkoxy,

C₁₋₄ alkoxy C₁₋₆ alkyl, hydroxycarbonyl, hydroxycarbonyl C₁₋₆ alkyl, C₁₋₅ alkoxycarbonyl, C₁₋₃ alkoxycarbonyl C₁₋₆ alkyl, hydroxycarbonyl C₁₋₆ alkyloxy, hydroxy, hydroxy C₁₋₆ alkyl, cyano, trifluoromethyl, oxo or C₁₋₅ alkylcarbonyloxy. Examples of aryl include, but are not limited to,

5 phenyl, naphthyl, pyridyl, pyrazinyl, pyrimidinyl, imidazolyl, benzimidazolyl, indolyl, thienyl, furyl, dihydrobenzofuryl, benzo(1,3) dioxolane, oxazolyl, isoxazolyl and thiazolyl, which are either unsubstituted or substituted with one or more groups independently selected from hydrogen, halogen, C₁₋₁₀ alkyl, C₃₋₈ cycloalkyl, aryl, aryl

10 C₁₋₈ alkyl, amino, amino C₁₋₈ alkyl, C₁₋₃ acylamino, C₁₋₃ acylamino C₁₋₈ alkyl, C₁₋₆ alkylamino, C₁₋₆ alkylamino-C₁₋₈ alkyl, C₁₋₆ dialkylamino, C₁₋₆ dialkylamino C₁₋₈ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkoxy C₁₋₆ alkyl, hydroxycarbonyl, hydroxycarbonyl C₁₋₆ alkyl, C₁₋₅ alkoxycarbonyl, C₁₋₃ alkoxycarbonyl C₁₋₆ alkyl, hydroxycarbonyl C₁₋₆ alkyloxy, hydroxy, hydroxy C₁₋₆ alkyl, cyano, trifluoromethyl, oxo or C₁₋₅ alkylcarbonyloxy. Preferably, the aryl group is unsubstituted, mono-, di-, tri- or tetra-substituted with one to four of the above-named substituents; more preferably, the aryl group is unsubstituted, mono-, di- or tri-substituted with one to three of the above-named substituents;

20 most preferably, the aryl group is unsubstituted, mono- or di-substituted with one to two of the above-named substituents.

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., aryl C₀₋₈ alkyl) it shall be interpreted as including those limitations given above for "alkyl" and

25 "aryl." Designated numbers of carbon atoms (e.g., C₁₋₁₀) shall refer independently to the number of carbon atoms in an alkyl or cyclic alkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

The terms "arylalkyl" and "alkylaryl" include an alkyl

30 portion where alkyl is as defined above and to include an aryl portion where aryl is as defined above. The C_{0-m} or C_{1-m} designation where m may be an integer from 1-10 or 2-10 respectively refers to the alkyl component of the arylalkyl or alkylaryl unit. Examples of arylalkyl include, but are not limited to, benzyl, fluorobenzyl, chlorobenzyl,

phenylethyl, phenylpropyl, fluorophenylethyl, chlorophenylethyl, thienylmethyl, thienylethyl, and thienylpropyl. Examples of alkylaryl include, but are not limited to, toluene, ethylbenzene, propylbenzene, methylpyridine, ethylpyridine, propylpyridine and butylpyridine.

- 5 When substituent R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³ or R¹⁴ includes the definition C₀ (e.g., aryl C₀₋₈ alkyl), the group modified by C₀ is not present in the substituent. Similarly, when any of the variables m, q, r or s is zero, then the group modified by the variable is not present; for example, when s is zero, the group "-(CH₂)_s C≡CH" is "-C≡CH".
- 10

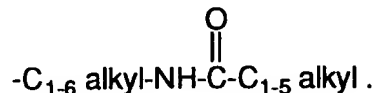
The term "halogen" shall include iodine, bromine, chlorine and fluorine.

- The term "oxy" means an oxygen (O) atom. The term "thio" means a sulfur (S) atom. The term "oxo" shall mean a bivalent oxygen atom (=O).
- 15

- The term "L- or D-amino acids" means naturally occurring L- or D-amino acids, for example, those naturally occurring L-amino acids present in humans, e.g. protein amino acids,, including L-alanine, L-arginine, L-asparagine, L-aspartic acid, L-cysteine, L-glutamine, L-glutamic acid, L-glycine, L-histidine, L-isoleucine, L-leucine, L-lysine, L-methionine, L-phenylalanine, L-proline, L-serine, L-threonine, L-tryptophan, L-tyrosine, and L-valine, and those naturally occurring D-amino acids which are non-protein amino acids, such as those found, for example, in antibiotic substances produced by bacteria and fungi, including D-valine, D-asparagine, D-glutamate, D-ornithine, D-phenylalanine, D-leucine, D-cysteine, and D-aspartate. (see Zubay "BIOCHEMISTRY" Addison-Wesley Publishing Company, Inc. (Reading, MA) 1983 pp. 867-870 and Stryer "BIOCHEMISTRY" W.H. Freeman and Company (New York, NY) 3rd Edition 1988 pp. 16-21).
- 20
- 25

- 30 The term "substituted" shall be deemed to include multiple degrees of substitution by a named substituent. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. For example, a C₁₋₅ alkylcarbonylamino C₁₋₆ alkyl substituent is equivalent to



The present invention is also directed to combinations of the compounds of the present invention with one or more agents useful in the prevention or treatment of osteoporosis. For example, the compounds of the instant invention may be effectively administered in combination with effective amounts of other agents used in the treatment of osteoporosis such as bisphosphonate bone resorption inhibitors; preferably, the bone resorption inhibitor is the bisphosphonate alendronate, now sold as FOSAMAX[®]. Preferred combinations are simultaneous or alternating treatments of an $\alpha\text{v}\beta 3$ receptor antagonist of the present invention and FOSAMAX[®]. In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating $\alpha\text{v}\beta 3$ related conditions includes in principle any combination with any pharmaceutical composition useful for treating osteoporosis.

Further exemplifying the invention are compositions further comprising an active ingredient selected from the group consisting of

- a.) an organic bisphosphonate or a pharmaceutically-acceptable salt or ester thereof,
- b.) an estrogen receptor modulator, and

c.) a cytotoxic/antiproliferative agent, and mixtures thereof.

Nonlimiting examples of such bisphosphonates include alendronate, etidronate, pamidronate, risedronate, and pharmaceutically acceptable salts and esters thereof. A particularly preferred bisphosphonate is alendronate, especially alendronate monosodium trihydrate.

Nonlimiting examples of estrogen receptor modulators include estrogen, progesterin, estradiol, raloxifene, and tamoxifene.

Nonlimiting examples of cytotoxic/antiproliferative agents are taxol and doxorubicin.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, topical (e.g., ocular eyedrop), subcutaneous, intramuscular or transdermal (e.g., patch) form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an $\alpha\beta3$ inhibitor.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician, veterinarian or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 100 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as 'carrier' materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be

combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable
5 binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium
10 benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small
15 unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the
20 compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted
25 with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polyactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters,
30 polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

In the schemes and examples below, various reagent symbols and abbreviations have the following meanings:

35 AcOH (HOAc): Acetic acid.

	BH ₃ •DMS:	Borane•dimethylsulfide.
	BOC(Boc):	t-Butyloxycarbonyl.
	BOP:	Benzotriazol-1-yloxytris(dimethylamino)- phosphonium hexafluorophosphate.
5	CBZ(Cbz):	Carbobenzyloxy or benzyloxycarbonyl.
	CDI:	Carbonyldiimidazole.
	CH ₂ Cl ₂ :	Methylene chloride.
	CHCl ₃ :	Chloroform.
	DEAD:	Diethyl azodicarboxylate.
10	DIAD:	Diisopropyl azodicarboxylate.
	DIBAH or DIBAL-H:	Diisobutylaluminum hydride.
	DIPEA:	Diisopropylethylamine.
	DMAP:	4-Dimethylaminopyridine.
15	DME:	1,2-Dimethoxyethane.
	DMF:	Dimethylformamide.
	DMSO:	Dimethylsulfoxide.
	DPFN:	3,5-Dimethyl-1-pyrazolylformamidine nitrate.
	EDC:	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide.
20	Et:	Ethyl.
	EtOAc:	Ethyl acetate.
	EtOH:	Ethanol.
	HOBT:	1-Hydroxybenzotriazole.
	LDA:	Lithium diisopropylamide.
25	MeOH:	Methanol.
	NEt ₃ :	Triethylamine.
	NMM:	N-methylmorpholine.
	PCA•HCl:	Pyrazole carboxamidine hydrochloride.
	Pd/C:	Palladium on activated carbon catalyst.
30	Pd(OAc) ₂ :	Palladium(II) acetate.
	Ph:	Phenyl.
	pTSA:	p-Toluene sulfonic acid.
	TEA:	Triethylamine.
	TFA:	Trifluoroacetic acid.

THF:	Tetrahydrofuran.
TLC:	Thin Layer Chromatography.
TMEDA:	N,N,N',N'-Tetramethylethylenediamine.
TMS:	Trimethylsilyl.
5 TsCl:	Tosyl chloride.

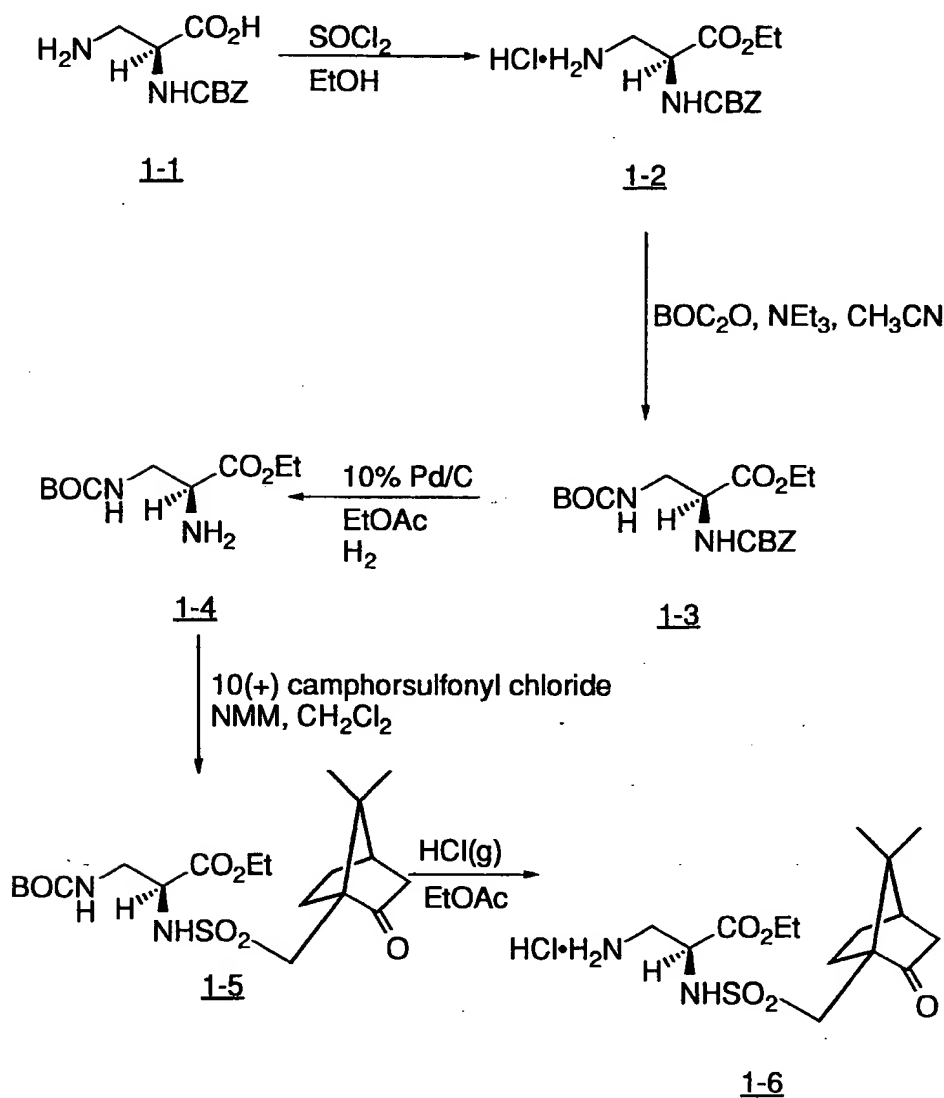
The novel compounds of the present invention were prepared according to the procedure of the following schemes and examples, using appropriate materials and are further exemplified by the following specific examples. The most preferred compounds of the invention are any or all of those specifically set forth in these examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless otherwise noted.

The following Schemes and Examples describe procedures for making representative compounds of the present invention. Moreover, by utilizing the procedures described in detail in PCT International Application Publication Nos. WO95/32710, published 7 December 1995, and WO95/17397, published 29 June 1995, in conjunction with the disclosure contained herein, one of ordinary skill in the art can readily prepare additional compounds of the present invention claimed herein.

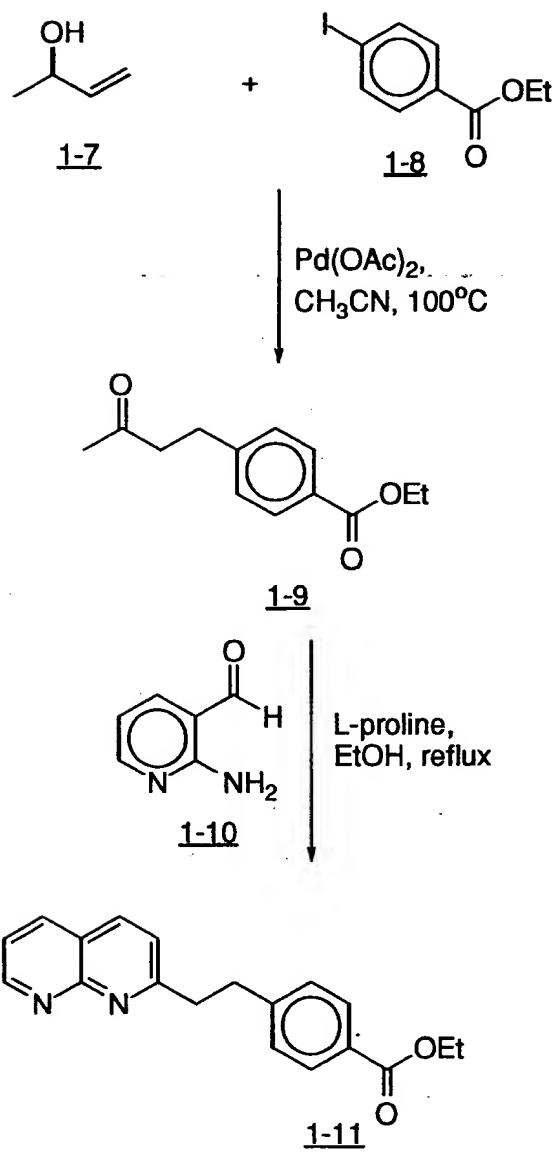
More specifically, procedures for preparing the N-terminus of the compounds of the present invention are described in WO 95/32710. Additionally, for a general review describing the synthesis of β -alanines which can be utilized as the C-terminus of the compounds of the present invention, see Cole, D.C., *Recent Stereoselective Synthetic Approaches to β -Amino Acids*, *Tetrahedron*, 1994, 50, 9517-9582; Juaristi, E, et al., *Enantioselective Synthesis of β -Amino Acids*, *Aldrichemica Acta*, 1994, 27, 3. In particular, synthesis of the 3-methyl β -alanine is taught in

- Duggan, M.F. et al., *J. Med. Chem.*, 1995, 38, 3332-3341; the 3-ethynyl β -alanine is taught in Zablocki, J.A., et al., *J. Med. Chem.*, 1995, 38, 2378-2394; the 3-pyrid-3-yl β -alanine is taught in Rico, J.G. et al., *J. Org. Chem.*, 1993, 58, 7948-7951; and the 2-amino and 2-tosylamino β -alanines are taught in Xue, C-B, et al., *Biorg. Med. Chem. Letts.*, 1996, 6, 339-344.

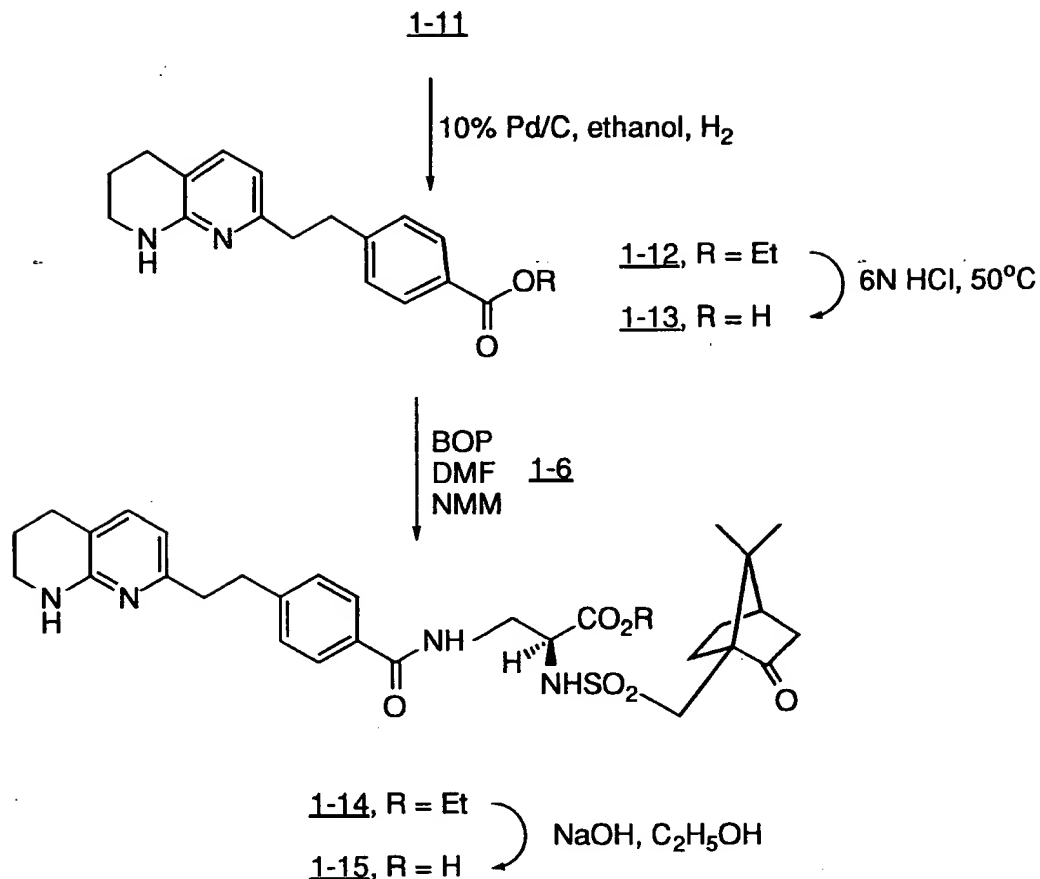
Scheme 1



Scheme 1 (continued)



Scheme 1 (continued)

Ethyl 2(S)-N α -Cbz-2,3-diaminopropionate hydrochloride (1-2)

- 1-1 (5 g, 21 mmol; Bachem) was dissolved in 100 mL EtOH and cooled to 0°C. SOCl₂ (9.2 mL, 126 mmol) was added followed by
- 5 removal of the cooling bath. After 6 hours, the reaction was concentrated to provide 1-2 as a white solid.
- ¹H NMR (300 MHz, CD₃OD) δ 7.35 (m, 5H), 5.14 (s, 2H), 4.44 (m, 1H), 4.22 (q, J=7Hz, 2H), 3.43 (m, 1H), 3.20 (m, 1H), 1.25 (t, J=7Hz, 3H).

Ethyl 2(S)-N α -Cbz-N β -Boc-2,3-diaminopropionate (1-3)

1-2 (2 g, 6.6 mmol) was dissolved in 60 mL CH₃CN. NEt₃ (1 mL, 7.2 mmol) was added followed by BOC₂O (1.58 g, 7.3 mmol). After two hours, the reaction was concentrated, diluted with EtOAc, washed with sat. NaHCO₃, 10% KHSO₄ and brine, dried (MgSO₄), filtered and concentrated to provide 1-3 as a clear oil.
TLC R_f 0.87 (silica, 80% EtOAc/hexanes).
¹H NMR (300 MHz, CDCl₃) δ 7.35 (s, 5H), 5.75 (bs, 1H), 5.12 (s, 2H), 4.81 (bs, 1H), 4.39 (m, 1H), 4.19 (m, 2H), 3.56 (m, 2H), 1.42 (s, 9H), 1.29 (q, J=7Hz, 3H).

Ethyl 2(S)-N β -Boc-2,3-diaminopropionate (1-4)

1-3 (2.4 g, 6.6 mmol) with 10% Pd/C (240 mg) in EtOAc (35 mL) was stirred under a H₂ atmosphere for 20 hours. The reaction was filtered through a celite pad and concentrated to provide 1-4 as a clear oil.
TLC R_f 0.13 (silica, 80% EtOAc/hexanes).
¹H NMR (300 MHz, CDCl₃) δ 5.00 (bs, 1H), 4.19 (m, 2H), 3.55 (m, 2H), 3.25 (m, 1H), 1.44 (s, 9H), 1.29 (q, J=7Hz, 3H).

Ethyl-2(S)-N α -(1(S)10-camphorsulfonylamino)-N β -Boc-2,3-diaminopropionate (1-5)

Amine 1-4 (760 mg, 3.27 mmol) was dissolved in 35 mL CH₂Cl₂ and cooled to 0°C. NMM (755 mL, 6.87 mmol) and 10(+) camphorsulfonyl chloride (1.23 g, 4.9 mmol; Aldrich) were added. After stirring at 0°C for one hour, the reaction was concentrated, then diluted with EtOAc, washed with H₂O, sat. NaHCO₃, 10% KHSO₄ and brine, dried (MgSO₄), and concentrated to an oil. Flash chromatography (silica, 25-40% EtOAc/hexanes) provided 1-5 as a clear oil.
TLC R_f 0.66 (silica, 50% EtOAc/hexanes).
¹H-NMR (300 MHz, CDCl₃) δ 6.37 (d, J=8Hz, 1H), 4.99 (bt, 1H), 4.32 (m, 1H), 4.23 (q, J=8Hz, 2H), 3.56 (m, 3H), 3.0 (d, J=15 Hz, 1H), 2.4 (m, 1H), 2.05 (m, 4H), 1.43 (s, 9H), 1.30 (t, J=7 Hz, 3H), 1.00 (s, 3H), 0.91 (s, 3H).

Ethyl-2(S)-N α -(1(S)10-camphorsulfonylamino)-2,3-diaminopropionate hydrochloride (1-6)

Ester 1-5 (900 mg, 2.18 mmol) was dissolved in 15 mL EtOAc and cooled to 0°C. HCl (g) was bubbled through the reaction mixture for 15 minutes. The reaction was removed from the cooling bath and purged with Ar (g) for 20 minutes followed by concentration to provide 1-6 as a foamy solid.

TLC R_f 0.05 (silica, 20% MeOH/EtOAc).

¹H-NMR (300 MHz, CDCl₃): δ 4.75 (m, 1H), 4.26 (q, J=7Hz, 2H), 3.50 (m, 4H), 2.40 (m, 3H), 1.98 (m, 4H), 1.30 (t, J=7Hz, 3H), 1.04 (s, 3H), 0.91 (s, 3H).

Ethyl 4-(3-oxo-butyl)benzoate (1-9)

3-Buten-2-ol 1-7 (2.15 mL, 25 mmol; Aldrich), ethyl 4-iodobenzoate 1-8 (5.5 g, 20 mmol, Aldrich) and NEt₃ (3.5 mL, 25 mmol) were combined in CH₃CN (6 mL) under argon in a pressure tube.

Pd(OAc)₂ (19 mg, 80 μ mol) was added and the reaction heated at 100°C for 3 hours. The reaction was cooled, then diluted with ether and washed with H₂O, 10% KHSO₄, sat. NaHCO₃, and brine, dried (MgSO₄), and concentrated to furnish 1-9 as a brown solid.

TLC R_f 0.23 (silica, 30% EtOAc/hexanes).

Ethyl 4-[2-(1,8-Naphthyridin-7-yl)ethyl]benzoate (1-11)

An ethanol solution (70 mL) of 1-10 (1.75 g, 14.3 mmol; JOC, 1983, 48, 3401-3408), 1-9 (3.15 g, 14.3 mmol, and L-proline (0.8 g, 7.0 mmol) was refluxed for 16 hours. The reaction was concentrated to dryness. Flash chromatography (silica, 60%-80% EtOAc/hexane) gave 1-11 as a yellow solid.

R_f 0.21 (silica, 3/1 EtOAc/hexane).

¹H NMR (300 MHz, CDCl₃) δ 9.1 (m, 1H), 8.18 (j, J=8 Hz, 1H), 8.08 (d, J=8 Hz, 1H), 7.95 (d, J=8 Hz, 2H), 7.48 (m, 1H), 7.30 (dd, J=8 Hz, 2H), 4.35 (q, J=7Hz, 2H), 3.35 (m, 4H), 1.38 (t, J=7Hz, 3H).

Ethyl 4-[2-(1,2,3,4-tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoate
(1-12)

- A mixture of 1-11 (645 mg, 2.1 mmol), 10% Pd/C (65 mg), and ethanol (10 mL) was stirred under a hydrogen atmosphere for 18 hour. Filtration
5 through a celite pad followed by concentration provided crude 1-12. Trituration of the solid with 1:1 ether/hexanes furnished 1-12 as a light yellow solid.
TLC R_f 0.75 (silica, 70% EtOAc/hexanes).
1H NMR (300 MHz, CDCl₃) δ 7.94 (d, J=8Hz, 2H), 7.26 (d, J=8 Hz, 2H),
10 7.03 (d, J=7 Hz, 1H), 6.28 (d, J=7 Hz, 1H), 4.81 (s, 1H), 4.35 (q, J=7 Hz, 2H),
3.40 (m, 2H), 3.03 (m, 2H), 2.84 (m, 2H), 2.69 (t, J=6 Hz, 2H), 1.93 (t, J=6
Hz, 2H), 1.38 (t, J=7 Hz, 3H).

4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoic acid (1-13)

- 15 The ester 1-12 (680 mg, 2.1 mmol) in 6N HCl (10 mL) was heated to 50⁰C for 18 hours. Concentration provided 1-13 as a light yellow solid.
1H NMR (300 MHz, CD₃OD) δ 7.93 (d, J=8 Hz, 2H), 7.52 (d, J=8 Hz, 1H),
7.31 (d, J=8 Hz, 2H), 5.54 (d, J=8 Hz, 1), 3.48 (t, J=5 Hz, 2H), 3.03 (m, 4H),
20 2.79 (t, J=6 Hz, 2H), 1.93 (t, J=6 Hz, 2H).

4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)[1(S)10-camphorsulfonylaminol β-alanine ethyl ester (1-14)

- 25 1-13 (200 mg, 0.627 mmol), amine 1-6 (240 mg, 0.69 mmol), NMM (345 mL, 3.13 mmol) and BOP reagent (332 mg, 0.75 mmol) were combined in 5 mL CH₃CN. After stirring overnight, the reaction was concentrated, then diluted with EtOAc, washed with H₂O, sat. NaHCO₃ and brine, dried (MgSO₄), filtered and concentrated. Flash
chromatography (silica, EtOAc) provided 1-14 as an off-white foamy
30 solid.
TLC R_f 0.13 (silica, EtOAc).
1H NMR (300 MHz, CDCl₃) δ 7.70 (d, J=8Hz, 2H), 7.25 (d, J=8Hz, 2H), 7.03
(d, J=7Hz, 1H), 6.72 (t, J=5Hz, 1H), 6.5 (bm, 1H), 6.28 (d, J=7Hz, 1H), 4.79
(s, 1H), 4.42 (bs, 1H), 4.25 (q, J=7Hz, 2H), 4.04 (m, 1H), 3.85 (m, 1H), 3.55

(d, J=15Hz, 1H), 3.41 (m, 2H), 3.00 (m, 3H), 2.82 (t, J=4Hz, 2H), 2.69 (t, J=6Hz, 2H), 2.04 (m, 8H), 1.58 (bs, 3H), 1.31 (t, J=7Hz, 3H), 1.00 (s, 3H), 0.90 (s, 3H).

5 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-
2(S)-[1(S)10-camphorsulfonylamino] β -alanine (1-15)

10 1-14 (250 mg, 0.409 mmol) was dissolved in 4 mL EtOH, 1M NaOH (1.02 mL, 1.02 mmol) was added and the reaction mixture was stirred for two hours. The reaction mixture was neutralized with 1N HCl and then concentrated to a foamy solid. Flash chromatography (silica, 18:10:1:1 EtOAc/EtOH/NH₄OH/H₂O) provided 1-15 as a slightly yellow solid.

TLC R_f 0.49 (silica, 12:10:1:1 EtOAc/EtOH/NH₄OH/H₂O).

15 ¹H NMR (400 MHz, DMSO) δ 8.48 (bt, 1H), 7.72 (d, J=8Hz, 2H), 7.55 (bs, 1H), 7.28 (d, J=8Hz, 2H), 7.02 (d, J=7Hz, 1H), 6.37 (s, 1H), 6.26 (d, J=7Hz, 1H), 4.13 (s, 1H), 3.54 (m, 3H), 3.37 (m, 2H), 2.94 (m, 3H), 2.73 (t, J=7Hz, 2H), 2.6 (t, J=6Hz, 2H), 2.3 (m, 3H), 2.02 (m, 1H), 1.89 (m, 2H), 1.75 (m, 2H), 1.49 (m, 1H), 1.37 (m, 1H), 1.05 (m, 1H), 0.95 (s, 3H), 0.66 (s, 3H).

20 Structurally related analogs of 1-15 can be prepared from commercially available starting materials utilizing the chemistry shown in Scheme 1. Several such representative compounds are exemplified as compounds 1-4 depicted in Table 1. Compounds 1 and 2 are readily available through the chemistry illustrated in Scheme 1 by
25 using 2(R)-N α -Cbz-2,3-diaminopropionic acid 5 (Bachem) or (1R)-(-)-10-camphorsulfonyl chloride 6 (Aldrich), respectively. Compounds 3 and 4 are attained by starting with the appropriate alcohols, 1-adamantanemethanol 7 (Aldrich) or (1R)-(-)-Nopol 8 (Aldrich),
30 respectively. These alcohols can be converted to their corresponding sulfonyl chlorides via the standard chemistry shown in Scheme 2.

Scheme 2

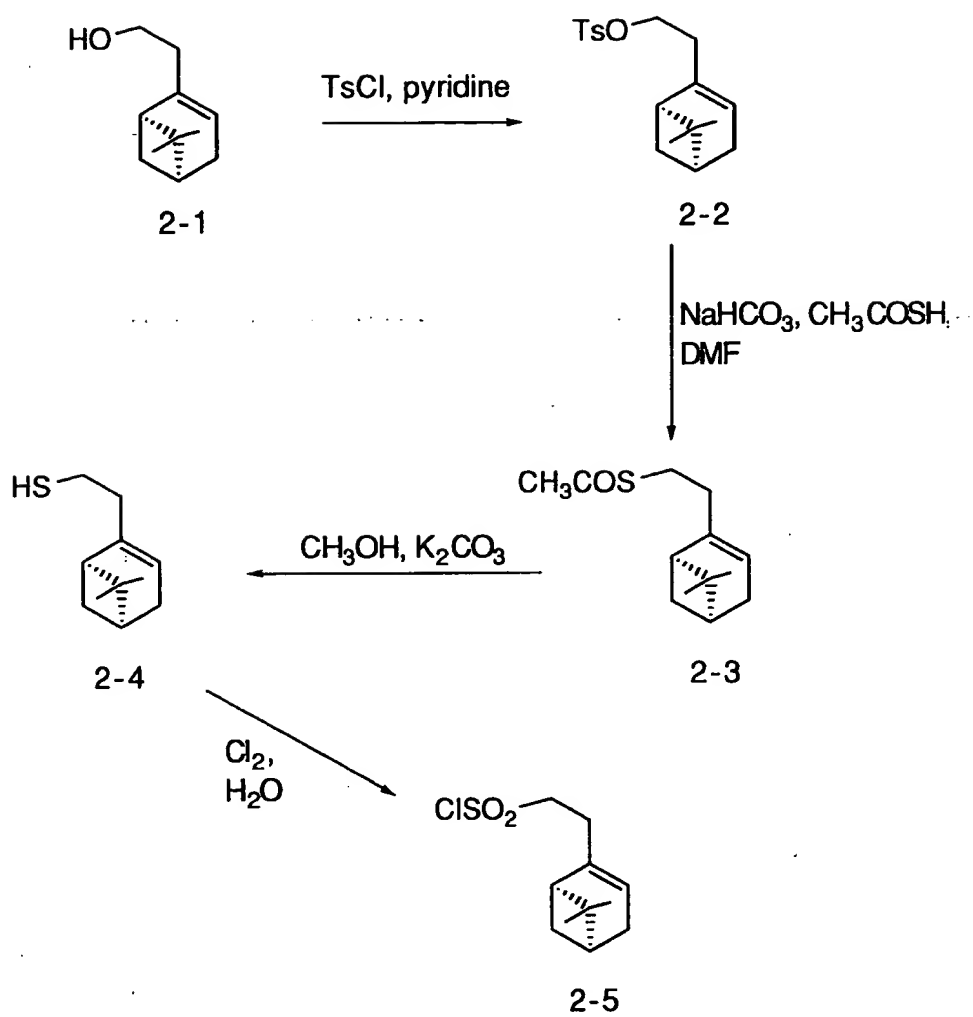
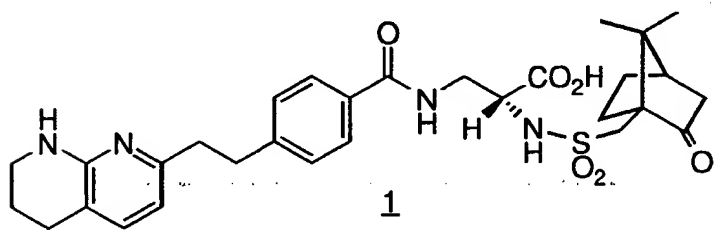
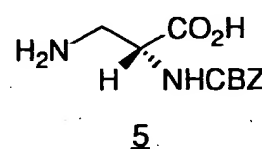
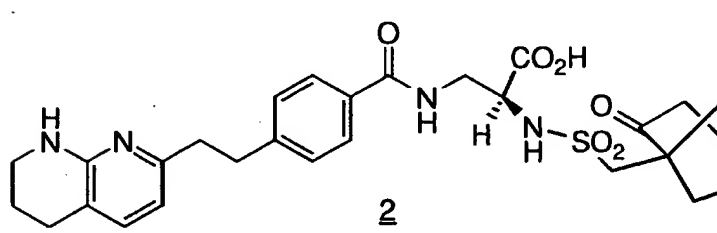
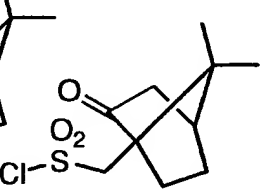
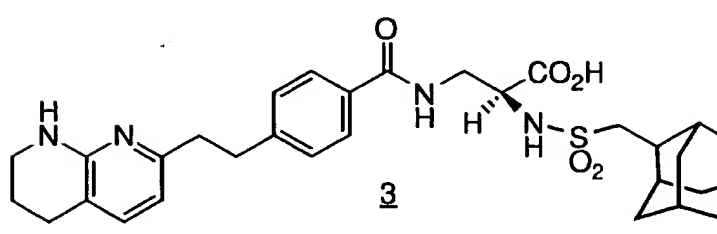
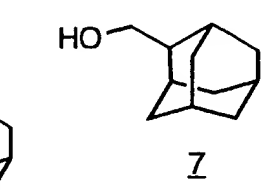
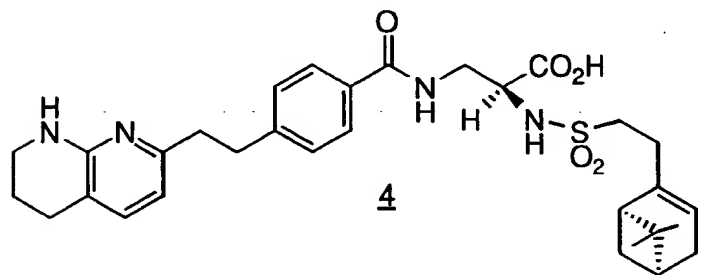
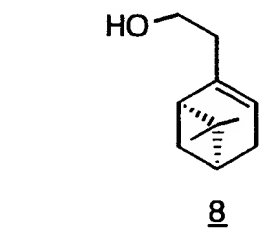
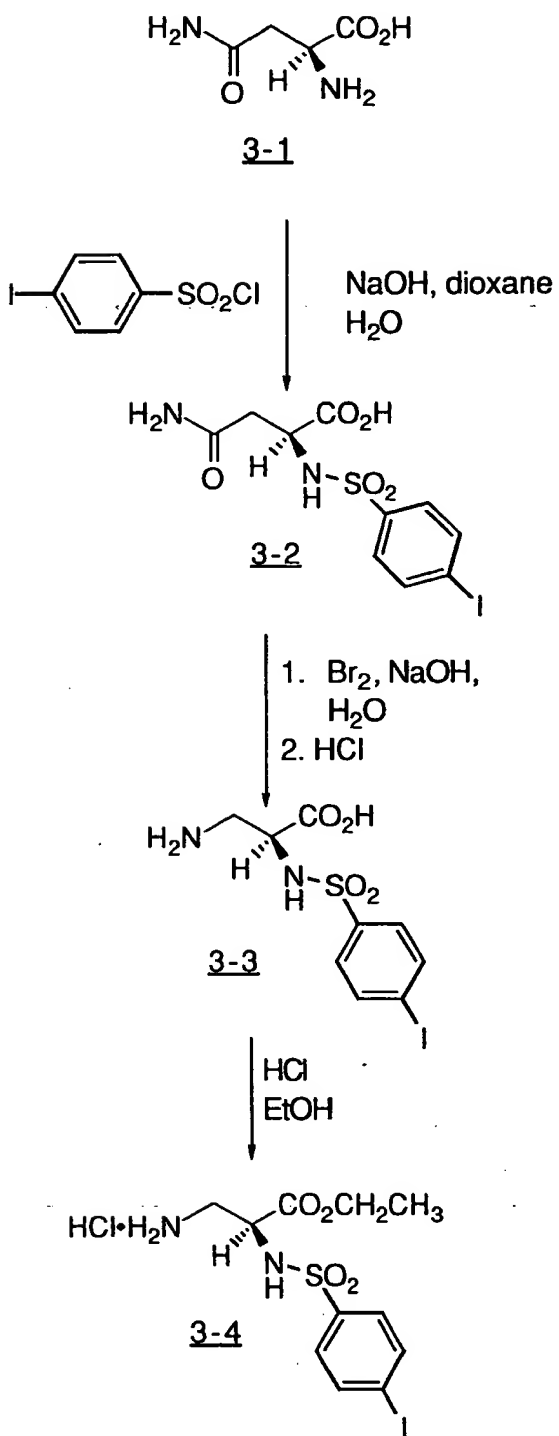


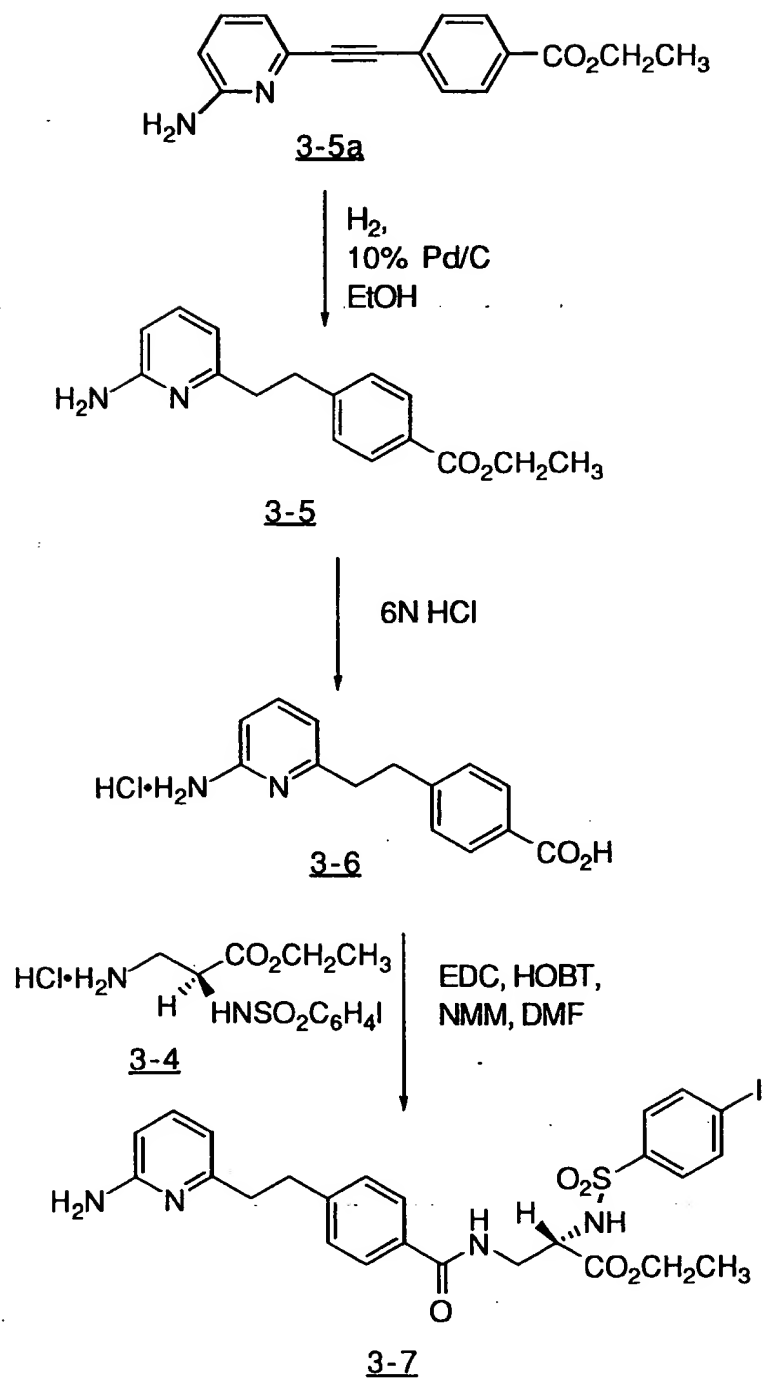
Table 1

Compound	Starting Material
 1	 5
 2	 6
 3	 7
 4	 8

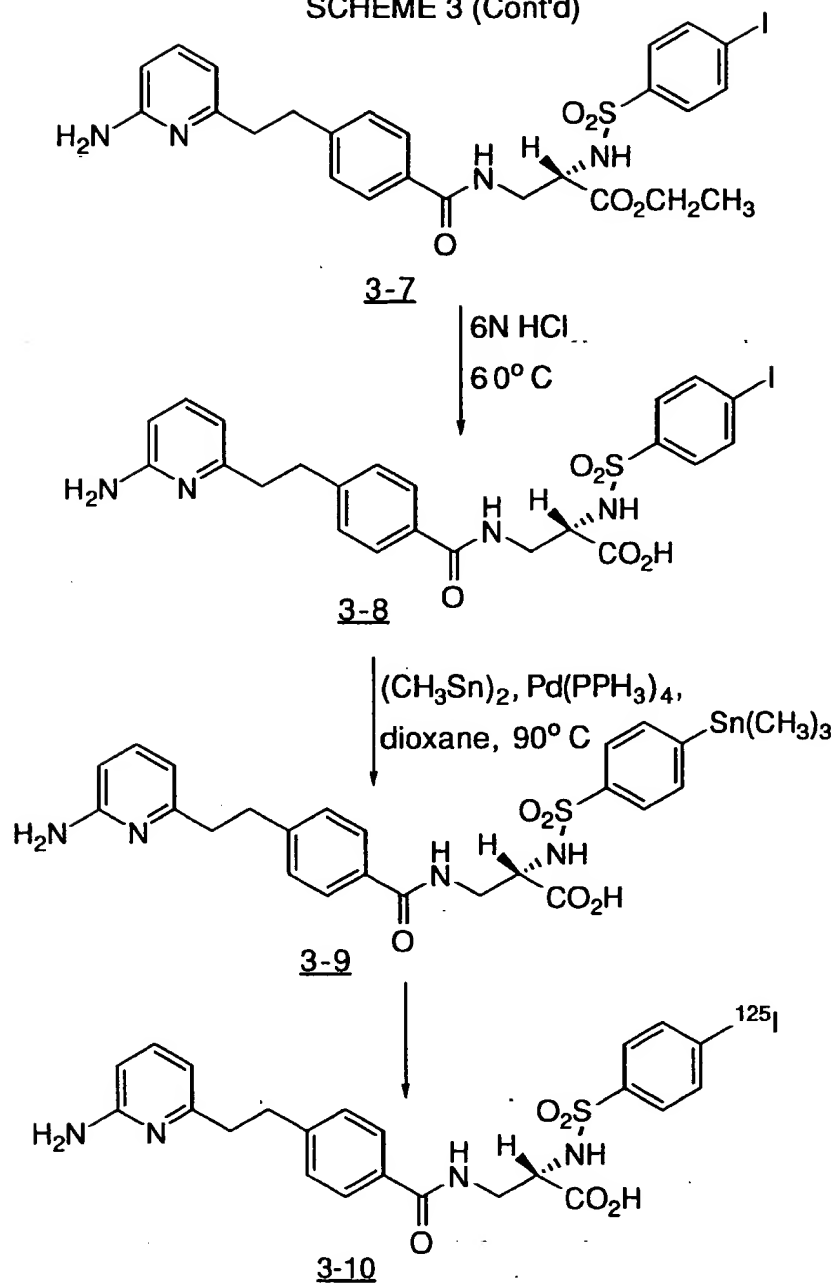
SCHEME 3



SCHEME 3 (Cont'd)



SCHEME 3 (Cont'd)



N-(4-Iodo-phenylsulfonylamino)-L-asparagine (3-2)

To a stirred solution of acid 3-1 (4.39 g, 33.2 mmol), NaOH (1.49 g, 37.2 mmol), dioxane (30 ml) and H₂O (30 ml) at 0°C was added pipsyl chloride (10.34 g, 34.2 mmol). After ~5 minutes, NaOH (1.49, 37.2 mmol) dissolved in 15 ml H₂O, was added followed by the removal of the cooling bath. After 2.0 h, the reaction mixture was concentrated. The residue was dissolved in H₂O (300 ml) and then washed with EtOAc.

The aqueous portion was cooled to 0°C and then acidified with concentrated HCl. The solid was collected and then washed with Et₂O to provide acid 3-2 as a white solid.

¹H NMR (300 MHz, D₂O) δ 7.86 (d, 2H, J=8Hz), 7.48 (d, 2H, J=8Hz) 3.70 (m, 1H), 2.39 (m, 2H).

2(S)-(4-Iodo-phenylsulfonylamino)-β-alanine (3-3)

To a stirred solution of NaOH (7.14 g, 181.8 mmol) and H₂O (40 ml) at 0°C was added Br₂ (1.30 ml, 24.9 mmol) dropwise over a ten minute period. After ~5 minutes, acid 3-2 (9.9 g, 24.9 mmol), NaOH (2.00 g, 49.8 mmol) and H₂O (35 ml) were combined, cooled to 0°C and then added in a single portion to the reaction. After stirring for 20 minutes at 0°C, the reaction was heated to 90°C for 30 minutes and then recooled to 0°C. The pH was adjusted to ~7 by dropwise addition of concentrated HCl. The solid was collected, washed with EtOAc, and then dried *in vacuo* to provide acid 3-3 as a white solid.

¹H NMR (300 MHz, D₂O) δ 8.02 (d, 2H, J=8Hz), 7.63 (d, 2H, J=8Hz), 4.36 (m, 1H), 3.51 (dd, 1H, J=5Hz, 13Hz) 3.21 (m, 1H).

Ethyl 2(S)-(4-iodo-phenylsulfonylamino)-β-alanine-hydrochloride (3-4)

HCl gas was rapidly bubbled through a suspension of acid 3-3 (4.0 g, 10.81 mmol) in EtOH (50 ml) at 0°C for 10 minutes. The cooling bath was removed and the reaction was heated to 60°C. After 18 h, the reaction was concentrated to provide ester 3-4 as a white solid.

¹H NMR (300 MHz, CD₃OD) δ 7.98 (d, 2H, J=8Hz), 7.63 (d, 2H, J=8Hz), 4.25 (q, 1H, J=5Hz), 3.92 (m, 2H), 3.33 (m, 1H), 3.06 (m, 1H), 1.01 (t, 3H, J=7Hz).

Ethyl 4-[2-(2-Aminopyridin-6-yl)ethyl]benzoate (3-5)

A mixture of ester 3-5a (700 mg, 2.63 mmol), (for preparation, see: Scheme 29 of PCT International Application Publication No. WO 95/32710, published December 7, 1995) 10% Pd/C (350 mg) and EtOH were stirred under 1 atm H₂. After 20 h, the reaction was filtered through a celite pad and then concentrated to provide ester 3-5 as a brown oil.

TLC R_f = 0.23 (silica, 40% EtOAc/hexanes)

¹H NMR (300 MHz, CDCl₃) δ 7.95 (d, 2H, J=8Hz), 7.26 (m, 3H), 6.43 (d, 1H, J=7Hz), 6.35 (d, 1H, J=8Hz), 4.37 (m, 4H), 3.05 (m, 2H), 2.91 (m, 2H), 1.39 (t, 3H, J=7Hz).

4-[2-(2-Aminopyridin-6-yl)ethyl]benzoic acid hydrochloride (3-6)

A suspension of ester 3-5 (625 mg, 2.31 mmol) in 6N HCl (12 ml) was heated to 60°C. After ~20 h, the reaction was concentrated to give acid 3-6 as a tan solid.

¹H NMR (300 MHz, CD₃OD) δ 7.96 (d, 2H, J=8Hz), 7.80 (m, 1H), 7.33 (d, 2H, J=8Hz), 6.84 (d, 1H, J=9Hz), 6.69 (d, 1H, J=7Hz), 3.09 (m, 4H).

Ethyl 4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-(4-iodophenyl)sulfonylamino)-β-alanine (3-7)

A solution of acid 3-6 (400 mg, 1.43 mmol), amine 3-4 (686 mg, 1.57 mmol), EDC (358 mg, 1.86 mmol), HOBT (252 mg, 1.86 mmol), NMM (632 μl, 5.72 mmol) and DMF (10 ml) was stirred for ~20 h. The reaction was diluted with EtOAc and then washed with sat NaHCO₃, brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, EtOAc to 5% isopropanol/EtOAc) provided amide 3-7 as a white solid.

TLC R_f = 0.4 (silica, 10% isopropanol/EtOAc)

¹H NMR (300 MHz, CD₃OD) δ 7.79 (d, 2H, J=9Hz), 7.61 (d, 2H, J=8Hz), 7.52 (d, 2H, J=9Hz), 7.29 (m, 1H), 7.27 (d, 2H, J=8Hz), 4.20 (m, 1H), 3.95 (q, 2H, J=7Hz), 3.66 (dd, 1H, J=6Hz, 14Hz), 3.49 (dd, 1H, J=8Hz, 13Hz), 3.01 (m, 2H), 2.86 (m, 2H), 1.08 (t, 3H, J=7Hz).

4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-(4-iodophenyl-sulfonylamino)- β -alanine (3-8)

A solution of ester 3-7 (200 mg, 0.3213 mmol) and 6N HCl (30 ml) was heated to 60°C. After ~20 h, the reaction mixture was concentrated. Flash chromatography (silica, 20:20:1:1 EtOAc/EtOH/NH₄OH/H₂O) provided acid 3-8 as a white solid.

TLC R_f = 0.45 (silica, 20:20:1:1 EtOAc/EtOH/NH₄OH/H₂O)

¹H NMR (400 MHz, DMSO) δ 8.40 (m, 1H), 8.14 (Bs, 1H), 7.81 (d, 2H, J=8Hz), 7.62 (d, 2H, J=8Hz), 7.48 (d, 2H, J=8Hz), 7.27 (m, 3H), 6.34 (d, 1H, J=7Hz), 6.25 (d, 1H, J=8Hz), 5.85 (bs, 2H), 3.89 (bs, 1H), 3.35 (m, 2H), 2.97 (m, 2H), 2.79 (m, 2H).

4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-(4-trimethylstannyl-phenylsulfonylamino)- β -alanine (3-9)

A solution of iodide 3-8 (70 mg, 0.1178 mmol), (CH₃Sn)₂ (49 μ l, 0.2356 mmol), Pd(PPh₃)₄ (5 mg) and dioxane (7 ml) was heated to 90°C. After 2 h, the reaction was concentrated and then purified by prep HPLC (Delta-Pak C₁₈ 15 μ M 100A°, 40 x 100 mm; 95:5 Δ 5:95 H₂O/CH₃CN) provided the trifluoroacetate salt. The salt was suspended in H₂O (10 ml), treated with NH₄OH (5 drops) and then lyophilized to provide amide 3-9 as a white solid.

¹H NMR (400 MHz, DMSO) δ 8.40 (m, 1H), 8.18 (d, 1H, J=8Hz), 7.67 (m, 5H), 7.56 (d, 2H, J=8Hz), 7.29 (d, 2H, J=8Hz), 6.95-7.52 (m, 2H), 6.45 (bs, 2H), 4.00 (m, 1H), 3.50 (m, 1H), 3.33 (m, 1H), 2.97 (m, 2H), 2.86 (m, 2H).

4-[2-(2-Aminopyridin-6-yl)ethyl]benzoyl-2(S)-4-¹²⁵Iodo-phenylsulfonylamino)- β -alanine (3-10)

An iodobead (Pierce) was added to a shipping vial of 5 mCi of Na¹²⁵I (Amersham, IMS30) and stirred for five minutes at room temperature. A solution of 0.1 mg of 3-9 in 0.05 mL of 10% H₂SO₄/MeOH was made and immediately added to the Na¹²⁵I/iodobead vial. After stirring for three minutes at room temperature, approximately 0.04-0.05 mL of NH₄OH was added so the reaction mixture was at pH 6-7. The entire reaction mixture was injected onto the HPLC for purification [Vydac peptide-protein C-18 column, 4.6 x 250 mm, linear gradient of

10% acetonitrile (0.1% (TFA):H₂O (0.1% TFA) to 90% acetonitrile (0.1% TFA):H₂O (0.1% TFA) over 30 minutes, 1 mL/min]. The retention time of 3-10 is 17 minutes under these conditions. Fractions containing the majority of the radioactivity were pooled, lyophilized and diluted with ethanol to give approximately 1 mCi of 3-10, which coeluted on HPLC analysis with an authentic sample of 3-8.

Instrumentation: Analytical and preparative HPLC was carried out using a Waters 600E Powerline Multi Solvent Delivery System with 0.1 mL heads with a Rheodyne 7125 injector and a Waters 990 Photodiode Array Detector with a Gilson FC203 Microfraction collector. For analytical and preparative HPLC a Vydac peptide-protein C-18 column, 4.6 x 250 mm was used with a C-18 Brownlee modular guard column. The acetonitrile used for the HPLC analyses was Fisher Optima grade. The HPLC radiodetector used was a Beckman 170 Radioisotope detector. A Vydac C-18 protein and peptide column, 3.9 x 250 mm was used for analytical and preparative HPLC. Solutions of radioactivity were concentrated using a Speedvac vacuum centrifuge. Calibration curves and chemical concentrations were determined using a Hewlett Packard Model 8452A UV/Vis Diode Array Spectrophotometer. Sample radioactivities were determined in a Packard A5530 gamma counter.

The test procedures employed to measure $\alpha v \beta 3$ binding and the bone resorption inhibiting activity of the compounds of the present invention are described below. In addition, the activity of the compounds of the present invention for treating cancer and/or inhibiting tumor growth is confirmed utilizing the nude mouse tumor xenograft assay described in Kohl et al., PNAS 91 (1994) 9141-45.

BONE RESORPTION-PIT ASSAY

When osteoclasts engage in bone resorption, they will literally cause the formation of pits in the surface of bone that they are acting upon. Therefore, when testing compounds for their ability to inhibit osteoclasts, it is useful to measure the ability of osteoclasts to excavate these resorption pits when the inhibiting compound is present.

Consecutive 200 micron thick cross sections from a six mm cylinder of bovine femur diaphysis were cut with a low speed diamond saw (Isomet, Beuler, Ltd., Lake Bluff, IL). Bone slices were pooled, placed in a 10% ethanol solution and refrigerated until further use.

Prior to experimentation, bone slices were ultrasonicated twice, 20 minutes each in H₂O. Cleaned slices were placed in 96 well plates such that two control lanes and one lane for each drug dosage are available. Each lane represents either triplicate or quadruplicate cultures. The bone slices in 96 well plates were sterilized by UV irradiation. Prior to incubation with osteoclasts, the bone slices were hydrated by the addition of 0.1 ml Medium 199, pH 6.9 containing 15% fetal bovine serum and 1% penicillin/streptomycin.

Osteoclasts were isolated from the long bones of 1 to 3 day old rat pups (Sprague-Dawley) by modifications of Chambers *et al.*, (*J. Cell. Science*, 66:383-399). The resulting suspension (0.75 ml/bone) was gently triturated 90-120 times using a wide bore transfer pipet. The cellular population was separated from bone fragments by a cell strainer with a 100 micron nylon mesh. 100 µl of the cell suspension was placed onto each bone slice. Test compounds were then added at the desired experimental concentrations.

Bone slices exposed to osteoclasts for 20-24 hrs were processed for staining. Tissue culture media was removed from each bone slice. Each well was washed with 200 µl of H₂O, and the bone slices were then fixed for 20 minutes in 2.5% glutaraldehyde, 0.1 M cacodylate, pH 7.4. After fixation, any remaining cellular debris was removed by 2 min. ultrasonication in the presence of 0.25 M NH₄OH followed by 2 X 15 min ultrasonication in H₂O. The bone slices were immediately stained for 6-8 min with filtered 1% toluidine blue and 1% borax.

After the bone slices have dried, resorption pits were counted in test and control slices. Resorption pits were viewed in a Microphot Fx (Nikon) fluorescence microscope using a polarizing Nikon IGS filter cube. Test dosage results were compared with controls and
5 resulting IC₅₀ values were determined for each compound tested.

The appropriateness of extrapolating data from this assay to utility and use in mammalian (including human) disease states is supported by the teaching found in Sato, M., et al., Journal of Bone and Mineral Research, Vol. 5, No. 1, 1990. That article teaches that certain
10 bisphosphonates have been used clinically and appear to be effective in the treatment of Paget's disease, hypercalcemia of malignancy, osteolytic lesions produced by bone metastases, and bone loss due to immobilization or sex hormone deficiency. These same
15 bisphosphonates are then tested in the resorption pit assay described above to confirm a correlation between their known utility and positive performance in the assay.

EIB ASSAY

Duong et al., J. Bone Miner. Res., 8:S 378, describe a system
20 for expressing the human integrin $\alpha v \beta 3$. It has been suggested that the integrin stimulates attachment of osteoclasts to bone matrix, since antibodies against the integrin, or RGD-containing molecules, such as echistatin (European Publication 382 451), can effectively block bone
25 resorption.

Reaction Mixture:

1. 175 μ l TBS buffer (50 mM Tris•HCl pH 7.2, 150 mM NaCl, 1% BSA, 1 mM CaCl₂, 1 mM MgCl₂).
2. 25 μ l cell extract (dilute with 100 mM octylglucoside buffer to
30 give 2000 cpm/25 μ l).
3. ¹²⁵I-echistatin (25 μ l/50,000 cpm) (see EP 382 451).
4. 25 μ l buffer (total binding) or unlabeled echistatin (non-specific binding).

The reaction mixture was then incubated for 1 h at room temp. The unbound and the bound $\alpha v\beta 3$ were separated by filtration using a Skatron Cell Harvester. The filters (prewet in 1.5% polyethyleneimine for 10 mins) were then washed with the wash buffer (50 mM Tris HCl, 1mM $\text{CaCl}_2/\text{MgCl}_2$, pH 7.2). The filter was then counted in a gamma counter.

SPA ASSAY

10 MATERIALS:

1. Wheatgerm agglutinin Scintillation Proximity Beads (SPA): Amersham
2. Octylglucopyranoside: Calbiochem
- 15 3. HEPES: Calbiochem
4. NaCl: Fisher
5. CaCl_2 : Fisher
6. MgCl_2 : SIGMA
7. Phenylmethylsulfonylfluoride (PMSF): SIGMA
- 20 8. Optiplate: PACKARD
9. 3-10 (specific activity 500-1000 Ci/mmol)
10. test compound
11. Purified integrin receptor: $\alpha v\beta 3$ was purified from 293 cells overexpressing $\alpha v\beta 3$ (Duong *et al.*, *J. Bone Min. Res.*, 8:S378, 1993) according to Pytela (*Methods in Enzymology*, 144:475, 1987)
- 25 12. Binding buffer: 50 mM HEPES, pH 7.8, 100 mM NaCl, 1 mM $\text{Ca}^{2+}/\text{Mg}^{2+}$, 0.5 mM PMSF
13. 50 mM octylglucoside in binding buffer: 50-OG buffer

30

PROCEDURE:

1. Pretreatment of SPA beads:
500 mg of lyophilized SPA beads were first washed four times with 200 ml of 50-OG buffer and once with 100 ml of binding buffer, and then resuspended in 12.5 ml of binding buffer.

35

2. Preparation of SPA beads and receptor mixture

5 In each assay tube, 2.5 µl (40 mg/ml) of pretreated beads were suspended in 97.5 µl of binding buffer and 20 ml of 50-OG buffer. 5 µl (~30 ng/µl) of purified receptor was added to the beads in suspension with stirring at room temperature for 30 minutes. The mixture was then centrifuged at 2,500 rpm in a Beckman GPR Benchtop centrifuge for 10 minutes at 4°C. The pellets were then resuspended in 50 µl of binding buffer and 25
10 µl of 50-OG buffer.

3. Reaction

The following were sequentially added into Optiplate in corresponding wells:

- 15 (i) Receptor/beads mixture (75 µl)
(ii) 25 µl of each of the following: compound to be tested, binding buffer for total binding or 3-8 for non-specific binding (final concentration 1 µM)
(iii) 3-10 in binding buffer (25 µl, final concentration 40 pM)
20 (iv) Binding buffer (125 µl)
(v) Each plate was sealed with plate sealer from PACKARD and incubated overnight with rocking at 4°C

4. Plates were counted using PACKARD TOPCOUNT
25

5. % inhibition was calculated as follows:

A = total counts

B = nonspecific counts

C = sample counts

30 % inhibition = $\frac{[(A-B)-(C-B)]}{(A-B)} \times 100$

OCFORM ASSAY

Osteoblast-like cells (1.8 cells), originally derived from mouse calvaria, were plated in CORNING 24 well tissue culture plates in α MEM medium containing ribo- and deoxyribonucleosides, 10% fetal bovine serum and penicillin-streptomycin. Cells were seeded at 40,000/well in the morning. In the afternoon, bone marrow cells were prepared from six week old male Balb/C mice as follows:

Mice were sacrificed, tibiae removed and placed in the above medium. The ends were cut off and the marrow was flushed out of the cavity into a tube with a 1 mL syringe with a 27.5 gauge needle. The marrow was suspended by pipetting up and down. The suspension was passed through $>100\ \mu\text{m}$ nylon cell strainer. The resulting suspension was centrifuged at $350 \times g$ for seven minutes. The pellet was resuspended, and a sample was diluted in 2% acetic acid to lyse the red cells. The remaining cells were counted in a hemacytometer. The cells were pelleted and resuspended at 1×10^6 cells/mL. 50 μL was added to each well of 1.8 cells to yield 50,000 cells/well and 1,25-dihydroxy-vitamin D₃(D₃) was added to each well to a final concentration of 10 nM. The cultures were incubated at 37°C in a humidified, 5% CO₂ atmosphere. After 48 h, the medium was changed. 72 h after the addition of bone marrow, test compounds were added with fresh medium containing D₃ to quadruplicate wells. Compounds were added again after 48 h with fresh medium containing D₃. After an additional 48 h the medium was removed, cells were fixed with 10% formaldehyde in phosphate buffered saline for 10 minutes at room temperature, followed by a 1-2 minute treatment with ethanol:acetone (1:1) and air dried. The cells were then stained for tartrate resistant acid phosphatase as follows:

The cells were stained for 10-15 minutes at room temperature with 50 mM acetate buffer, pH 5.0 containing 30 mM sodium tartrate, 0.3 mg/mL Fast Red Violet LB Salt and 0.1 mg/mL Naphthol AS -MX phosphate. After staining, the plates were washed extensively with deionized water and air dried. The number of multinucleated, positive staining cells were counted in each well.

EXAMPLE OF A PHARMACEUTICAL FORMULATION

As a specific embodiment of an oral composition, 100 mg of compound 1 (shown in Table 1) is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

While the invention has been described and illustrated in reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred doses as set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the mammal being treated for severity of bone disorders caused by resorption, or for other indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

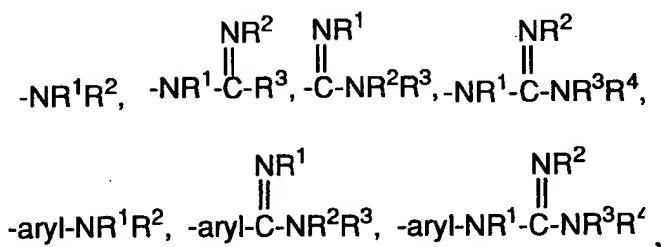
1. A compound of the formula



wherein:

10 Aryl is a 6-membered aromatic ring containing 0, 1, 2 or 3 nitrogen atoms and either unsubstituted or substituted with R^8 and R^9 ;

X is selected from



15 a 5- or 6-membered monocyclic aromatic or nonaromatic ring system containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O or S wherein the 5- or 6-membered ring system is either unsubstituted or substituted with R^1 , R^2 , R^3 and R^4 , or

20 a 9- to 14-membered polycyclic ring system, wherein one or more of the rings is aromatic, and wherein the polycyclic ring system contains 0, 1, 2, 3 or 4 heteroatoms selected from N, O or S, and wherein the polycyclic ring system is either unsubstituted or substituted with R^1 , R^2 , R^3 and R^4 ;

25

Y is selected from

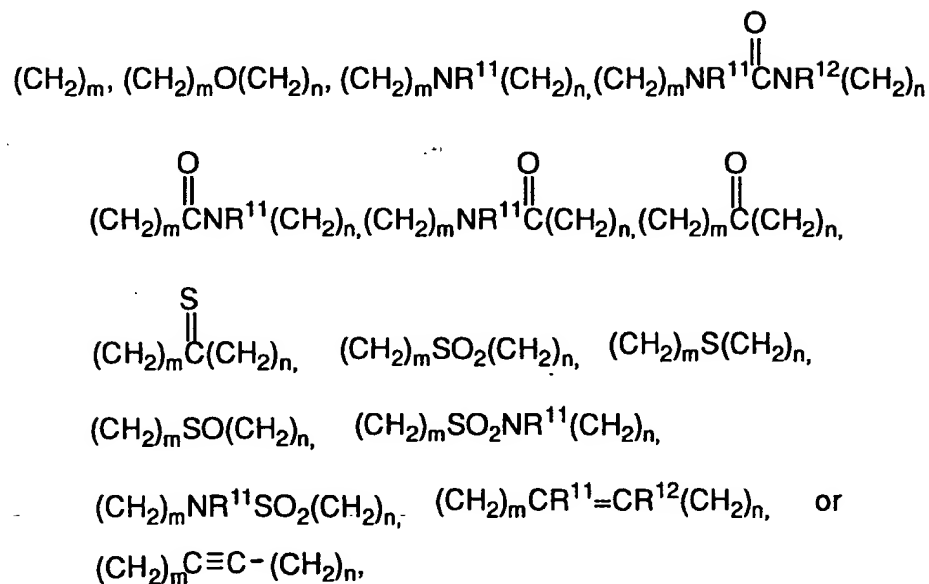
C0-8 alkylene,

C3-10 cycloalkyl,

- C₀₋₈ alkylene-NR¹⁰-CO-C₀₋₈ alkylene,
 C₀₋₈ alkylene-CONR¹⁰-C₀₋₈ alkylene,
 C₀₋₈ alkylene-O-C₀₋₈ alkylene,
 C₀₋₈ alkylene-NR¹⁰-C₀₋₈ alkylene,
 5 C₀₋₈ alkylene-S(O)₀₋₂-C₀₋₈ alkylene,
 C₀₋₈ alkylene-SO₂-NR¹⁰-C₀₋₈ alkylene,
 C₀₋₈ alkylene-NR¹⁰-SO₂-C₀₋₈ alkylene,
 C₀₋₈ alkylene-CO-C₀₋₈ alkylene,
 (CH₂)₀₋₆ aryl(CH₂)₀₋₆,
 10 (CH₂)₀₋₆ aryl-CO-(CH₂)₀₋₆,
 (CH₂)₀₋₆ aryl-CO-NR¹⁰-(CH₂)₀₋₆,
 (CH₂)₀₋₆ arylNR¹⁰CO(CH₂)₀₋₆, or

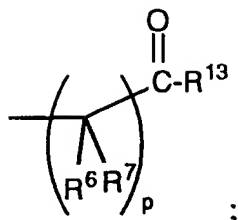
$$\begin{array}{c} \text{OR}^1 \\ | \\ (\text{CH}_2)_{0-8}\text{CH}(\text{CH}_2)_{0-8} \end{array}$$

- 15 Z and A are each independently selected from



where m and n are each independently an integer from 0 to 6;

B is



where p is an integer from 1 to 3;

R¹, R², R³, R⁴, R⁵, R⁸, R⁹, R¹⁰, R¹¹ and R¹² are each independently

5 selected from

- hydrogen,
- halogen,
- C₁₋₁₀ alkyl,
- aryl C₀₋₈ alkyl,
- 10 amino C₀₋₈ alkyl,
- C₁₋₃ acylamino C₀₋₈ alkyl,
- C₁₋₆ alkylamino C₀₋₈ alkyl,
- C₁₋₆ dialkylamino C₀₋₈ alkyl,
- aryl C₀₋₆ alkylamino C₀₋₆ alkyl,
- 15 C₁₋₄ alkoxyamino C₀₋₈ alkyl,
- hydroxy C₁₋₆ alkylamino C₀₋₈ alkyl,
- C₁₋₄ alkoxy C₀₋₆ alkyl,
- hydroxycarbonyl C₀₋₆ alkyl,
- C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl,
- 20 hydroxycarbonyl C₀₋₆ alkyloxy,
- hydroxy C₁₋₆ alkylamino C₀₋₆ alkyl, or
- hydroxy C₀₋₆ alkyl;

R⁶ is selected from

- 25 hydrogen,
- fluorine,
- C₁₋₈ alkyl,
- hydroxyl,
- hydroxy C₁₋₆ alkyl,
- 30 carboxy C₀₋₆ alkyl,

- 5 C₁₋₆ alkyloxy,
C₁₋₆ alkylcarbonyl,
aryl C₀₋₆ alkylcarbonyl,
C₁₋₆ alkylcarbonyloxy,
aryl C₀₋₆ alkylcarbonyloxy,
C₁₋₆ alkylaminocarbonyloxy,
C₃₋₈ cycloalkyl,
aryl C₀₋₆ alkyl,
C₀₋₆ alkylamino C₀₋₆ alkyl,
10 C₀₋₆ dialkylamino C₀₋₆ alkyl,
C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl,
aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl,
C₁₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
aryl C₀₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
15 C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,
aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,
C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
aryl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
20 aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,
aryl C₀₋₆ alkylsulfonyl C₀₋₆ alkyl,
C₁₋₆ alkylcarbonyl C₀₋₆ alkyl,
aryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl,
25 C₁₋₆ alkylthiocarbonylamino C₀₋₆ alkyl, or
aryl C₀₋₆ alkylthiocarbonylamino C₀₋₆ alkyl;
wherein the alkyl or N atoms may be unsubstituted or
substituted with R⁵;
- 30 R⁷ is selected from
C₇₋₂₀ polycyclyl C₀₋₈ alkylsulfonylamino C₀₋₆ alkyl;
C₇₋₂₀ polycyclyl C₀₋₈ alkylcarbonylamino C₀₋₆ alkyl;
C₇₋₂₀ polycyclyl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl;
C₇₋₂₀ polycyclyl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl or

C7-20 polycyclyl C0-8 alkyloxycarbonylamino C0-6 alkyl;
wherein the polycyclyl may be unsubstituted or substituted with
R¹⁴, R¹⁵, R¹⁶ and R¹⁷; and wherein any of the alkyl groups may
be unsubstituted or substituted with R¹⁴ and R¹⁵;

5

R¹³ is selected from

hydroxy,
C₁₋₈ alkyloxy,
aryl C₀₋₆ alkyloxy,
10 C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy,
aryl C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy,
C₁₋₆ dialkylaminocarbonylmethyloxy,
aryl C₁₋₆ dialkylaminocarbonylmethyloxy or
an L- or D-amino acid joined by an amide linkage and
15 wherein the carboxylic acid moiety of said amino acid
is as the free acid or is esterified by C₁₋₆ alkyl; and

R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are each independently selected from
hydrogen, halogen, C₁₋₁₀ alkyl, C₃₋₈ cycloalkyl, oxo, aryl,
20 aryl C₁₋₈ alkyl, amino, amino C₁₋₈ alkyl, C₁₋₃ acylamino,
C₁₋₃ acylamino C₁₋₈ alkyl, C₁₋₆ alkylamino, C₁₋₆ alkylamino-
C₁₋₈ alkyl, C₁₋₆ dialkylamino, C₁₋₆ dialkylamino C₁₋₈ alkyl,
C₁₋₄ alkoxy, C₁₋₄ alkoxy C₁₋₆ alkyl, hydroxycarbonyl,
hydroxycarbonyl C₁₋₆ alkyl, C₁₋₃ alkoxycarbonyl,
25 C₁₋₃ alkoxycarbonyl C₁₋₆ alkyl, hydroxycarbonyl-
C₁₋₆ alkyloxy, hydroxy, hydroxy C₁₋₈ alkyl, C₁₋₆ alkyloxy-
C₁₋₆ alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy,
trifluoroethoxy, C₁₋₈ alkyl-S(O)_q, C₁₋₈ alkylaminocarbonyl,
C₁₋₈ dialkylaminocarbonyl, C₁₋₈ alkyloxycarbonylamino,
30 C₁₋₈ alkylaminocarbonyloxy or C₁₋₈ alkylsulfonylamino;

and the pharmaceutically acceptable salts thereof;

provided that the compound is not 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamino] β -alanine ethyl ester (1-14) or 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamino] β -alanine (1-15).

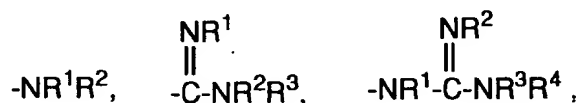
5

2. The compound of Claim 1, wherein

Aryl is a 6-membered aromatic ring containing 0, 1 or 2 nitrogen atoms wherein Aryl is unsubstituted or substituted with R^8 and R^9 ;

10

X is selected from



15

a 5- or 6-membered monocyclic aromatic or nonaromatic ring system containing 0, 1 or 2 heteroatoms selected from N, O or S wherein the 5- or 6-membered ring system is either unsubstituted or substituted with R^1 and R^2 , or

20

a 9- to 14-membered fused polycyclic ring system, wherein one or more of the rings is aromatic, and wherein the polycyclic ring system contains 0, 1, 2 or 3 heteroatoms selected from N, O or S, and wherein the polycyclic ring system is either unsubstituted or substituted with R^1 and R^2 ;

25

Y is selected from the group consisting of

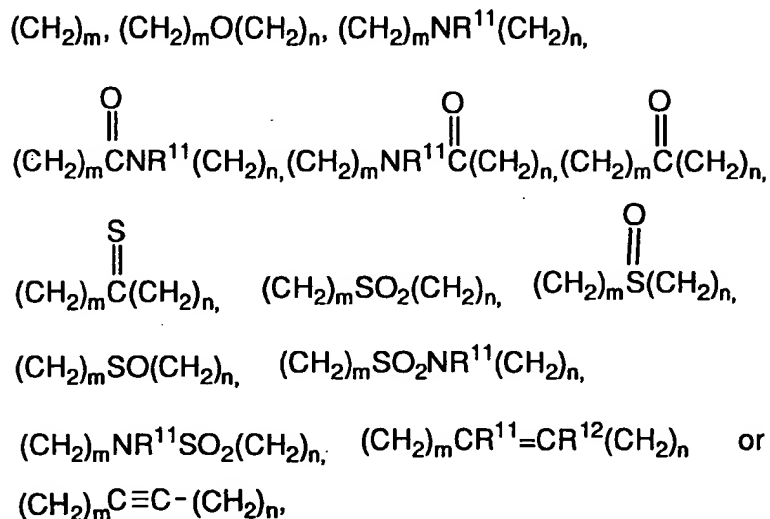
30

C₀₋₈ alkylene,
C₃₋₁₀ cycloalkyl,
C₀₋₈ alkylene-NR¹⁰-CO-C₀₋₈ alkylene,
C₀₋₈ alkylene-CONR¹⁰-C₀₋₈ alkylene,
C₀₋₈ alkylene-O-C₀₋₈ alkylene,
C₀₋₈ alkylene-NR¹⁰-C₀₋₈ alkylene,
C₀₋₈ alkylene-S(O)₀₋₂-C₀₋₈ alkylene,
C₀₋₈ alkylene-SO₂-NR¹⁰-C₀₋₈ alkylene,

- C0-8 alkylene-NR¹⁰-SO₂-C0-8 alkylene,
 C0-8 alkylene-CO-C0-8 alkylene,
 (CH₂)₀₋₆ aryl(CH₂)₀₋₆,
 (CH₂)₀₋₆ aryl-CO-(CH₂)₀₋₆,
 5 (CH₂)₀₋₆ aryl-CO-NH-(CH₂)₀₋₆, or

$$\begin{array}{c} \text{OR}^1 \\ | \\ (\text{CH}_2)_{0-8}\text{CH}(\text{CH}_2)_{0-8} \end{array}$$

Z and A are each independently selected from



- 10 where m and n are each independently an integer from 0 to 4;

R¹, R², R³, R⁴, R⁵, R⁸, R⁹, R¹⁰, R¹¹ and R¹² are each independently selected from

- hydrogen,
 15 halogen,
 C1-10 alkyl,
 aryl C0-8 alkyl,
 amino C0-8 alkyl,
 C1-3 acylamino C0-8 alkyl,
 20 C1-6 alkylamino C0-8 alkyl,
 C1-6 dialkylamino C0-8 alkyl,

5 aryl C₀₋₆ alkylamino C₀₋₆ alkyl,
C₁₋₄ alkoxyamino C₀₋₈ alkyl,
hydroxy C₁₋₆ alkylamino C₀₋₈ alkyl,
C₁₋₄ alkoxy C₀₋₆ alkyl, or
C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl;

10 R⁶ is selected from
hydrogen,
C₁₋₈ alkyl or
aryl C₀₋₆ alkyl;

15 R⁷ is selected from
C₇₋₁₅ polycyclyl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl or
C₇₋₁₅ polycyclyl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl;
wherein the polycyclyl may be unsubstituted or substituted with
R¹⁴, R¹⁵, R¹⁶ and R¹⁷; and wherein any of the alkyl groups may
be unsubstituted or substituted with R¹⁴ and R¹⁵;

20 and the pharmaceutically acceptable salts thereof;

provided that the compound is not 4-[2-(1,2,3,4-Tetrahydro-1,8-
naphthyridin-7-yl)ethyl]benzoyl-2(S)[1(S)10-camphorsulfonylamino] β-
alanine ethyl ester (1-14) or 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-
yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamino] β-alanine (1-15).

25 3. The compound of Claim 2, wherein

30 Aryl is a phenyl or pyridyl ring which is unsubstituted or substituted
with R⁸;

X is

a 9- to 14-membered fused polycyclic ring system, wherein one or
more of the rings is aromatic, and wherein the polycyclic ring
system contains 0, 1, 2 or 3 heteroatoms selected from N, O or S,

and wherein the polycyclic ring system is either unsubstituted or substituted with R^1 and R^2 ;

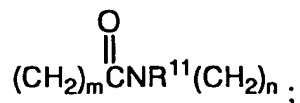
Y is selected from

- 5 C0-6 alkylene,
 C0-6 alkylene- NR^{10} -CO-C0-6 alkylene,
 C0-6 alkylene-CONR¹⁰-C0-6 alkylene,
 C0-6 alkylene-O-C0-6 alkylene,
 C0-6 alkylene- NR^{10} -C0-6 alkylene,
 10 C0-6 alkylene-S(O)₀₋₂-C0-6 alkylene,
 C0-6 alkylene-SO₂- NR^{10} -C0-6 alkylene, or
 C0-6 alkylene-aryl-C0-6 alkylene;

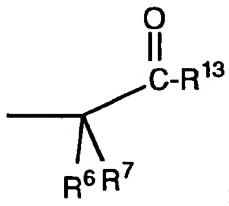
Z is selected from

- 15 $(CH_2)_m$, $(CH_2)_mO(CH_2)_n$ or $(CH_2)_mNR^{11}\overset{O}{\parallel}C(CH_2)_n$;

A is



20 B is



R^1 , R^2 , R^3 , R^4 , R^5 , R^8 , R^9 , R^{10} , R^{11} and R^{12} are each independently selected from

hydrogen,
halogen,
C₁₋₁₀ alkyl,
aryl C₀₋₈ alkyl,
5 C₁₋₄ alkoxy C₀₋₆ alkyl, or
C₁₋₄ alkoxycarbonyl C₀₋₆ alkyl;

R⁶ is hydrogen;

10 R⁷ is selected from
C₇₋₁₀ polycyclyl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl or
C₇₋₁₀ polycyclyl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl;
wherein the polycyclyl may be unsubstituted or substituted with
R¹⁴, R¹⁵, R¹⁶ and R¹⁷;

15 R¹³ is selected from
hydroxy or
C₁₋₈ alkyloxy;

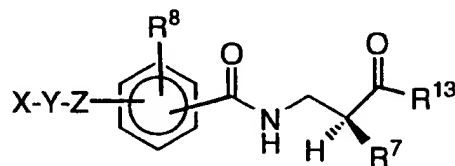
20 R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are each independently selected from
hydrogen, halogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, oxo, amino,
amino C₁₋₈ alkyl, C₁₋₃ acylamino, C₁₋₃ acylamino C₁₋₈ alkyl,
C₁₋₆ alkylamino, C₁₋₆ alkylamino C₁₋₈ alkyl,
C₁₋₆ dialkylamino, C₁₋₆ dialkylamino C₁₋₈ alkyl,
25 C₁₋₄ alkoxy, C₁₋₄ alkoxy C₁₋₆ alkyl, hydroxycarbonyl,
hydroxycarbonyl C₁₋₆ alkyl, C₁₋₃ alkoxycarbonyl,
C₁₋₃ alkoxycarbonyl C₁₋₆ alkyl, hydroxycarbonyl-
C₁₋₆ alkyloxy, hydroxy, hydroxy C₁₋₆ alkyl, C₁₋₆ alkyloxy-
C₁₋₆ alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy,
30 trifluoroethoxy, C₁₋₈ alkylsulfonyl, C₁₋₈ alkylaminocarbonyl,
C₁₋₈ alkyloxycarbonylamino, C₁₋₈ alkylaminocarbonyloxy or
C₁₋₈alkylsulfonylamino;

and the pharmaceutically acceptable salts thereof;
35

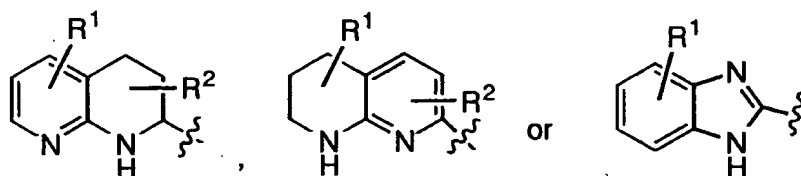
provided that the compound is not 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)[1(S)10-camphorsulfonylamino] β -alanine ethyl ester (1-14) or 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamino] β -alanine (1-15).

5

4. The compound of Claim 3, of the formula:



wherein X is selected from the group consisting of



10 Y is selected from
C₀₋₆ alkylene,
C₀₋₆ alkylene-O-C₀₋₆ alkylene or
C₀₋₆ alkylene-NR¹⁰-C₀₋₆ alkylene;

15 Z is selected from



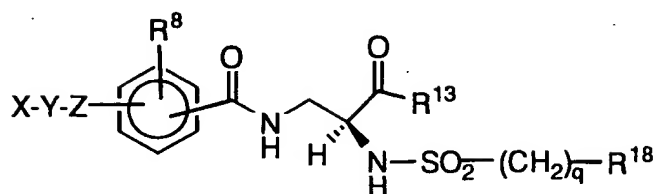
R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are each independently selected from
hydrogen, halogen, C₁₋₆ alkyl, oxo or hydroxy;

20 and the pharmaceutically acceptable salts thereof;

provided that the compound is not 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)[1(S)10-camphorsulfonylamino] β -alanine ethyl ester (1-14) or 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamino] β -alanine (1-15).

25

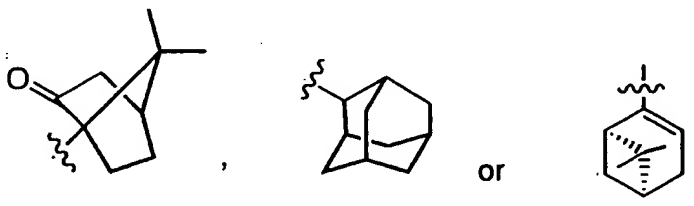
5. The compound of Claim 3, of the formula:



wherein

5 q is an integer from 0 to 2;

R¹⁸ is selected from



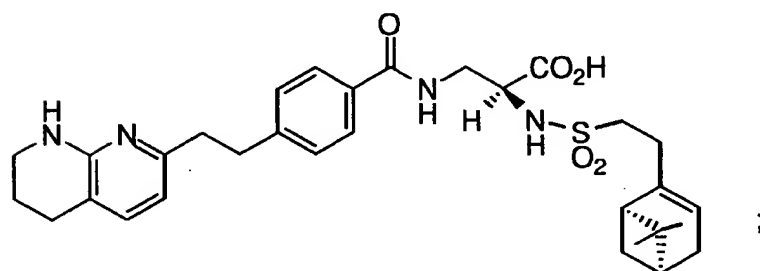
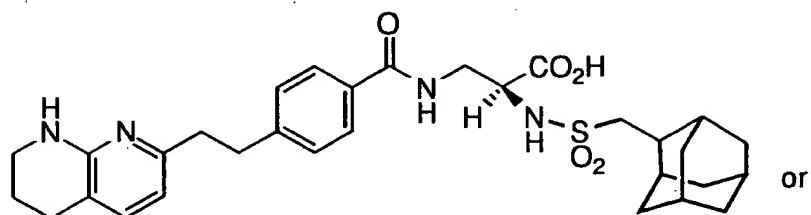
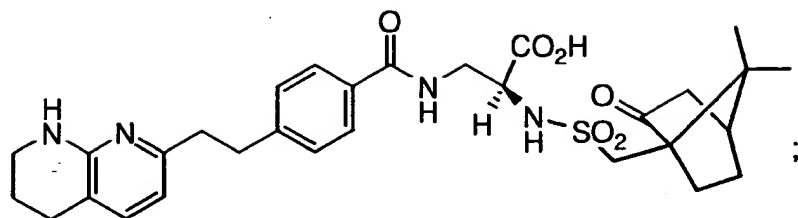
and the pharmaceutically acceptable salts thereof;

10

provided that the compound is not 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamino] β-alanine ethyl ester (1-14) or 4-[2-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)ethyl]benzoyl-2(S)-[1(S)10-camphorsulfonylamino] β-alanine (1-15).

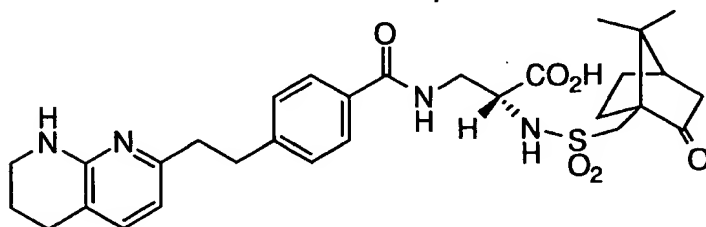
15

6. The compound of Claim 5, selected from



and the pharmaceutically acceptable salts thereof.

7. The compound of Claim 4, of the formula



5

and the pharmaceutically acceptable salts thereof.

8. A pharmaceutical composition comprising the compound of Claim 1 and a pharmaceutically acceptable carrier.

5 9. A pharmaceutical composition made by combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

10 10. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

11. A method of eliciting a vitronectin antagonizing effect in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1.

15 12. The method of Claim 11, wherein the vitronectin antagonizing effect is selected from inhibition of bone resorption, inhibition of restenosis, inhibition of angiogenesis, inhibition of atherosclerosis, inhibition of inflammation, inhibition of viral disease, inhibition of diabetic retinopathy, inhibition of macular degeneration or
20 inhibition of tumor growth.

13. The method of Claim 12, wherein the vitronectin antagonizing effect is the inhibition of tumor growth.

25 14. A method of treating or preventing a condition mediated by antagonism of a vitronectin receptor in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1.

30 15. The method of Claim 14, wherein the condition is selected from the group consisting of osteoporosis and cancer.

35 16. A method of inhibiting tumor growth in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1.

17. A method according to Claim 16 wherein said compound is administered in conjunction with radiation therapy.

5 18. A method of treating cancer in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1.

10 19. A method of eliciting a vitronectin antagonizing effect in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 8.

15 20. A method of treating or preventing a condition mediated by antagonism of a vitronectin receptor in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 8.

20 21. A method of inhibiting tumor growth in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 8.

25 22. A method of treating cancer in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 8.

30 23. A method of treating cancer in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1 and one or more agents known to be cytotoxic or antiproliferative.

35 24. A method of inhibiting angiogenesis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the compound of Claim 1 and a VEGF inhibitor compound.

25. A method according to claim 24 which further comprises treating a condition selected from cancer, macular degeneration, or diabetic retinopathy.

5

26. A composition according to Claim 8 which further comprises an active ingredient selected from the group consisting of

- a.) an organic bisphosphonate or a pharmaceutically-acceptable salt or ester thereof,
- 10 b.) an estrogen receptor modulator, and
- c.) a cytotoxic/antiproliferative agent, and mixtures thereof.

27. A composition according to Claim 26 wherein said organic bisphosphonate or pharmaceutically-acceptable salt or ester
15 thereof is alendronate monosodium trihydrate.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/00617

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95/32710 A1 (MERCK & CO., INC.) 07 December 1995, claims 1-25.	1-27
X	WO 94/12181 A1 (MERCK & CO., INC.) 09 June 1994, claim 1.	1-7
X	US 5,563,158 A (DEGRADO et al.) 08 October 1996, compounds in Tables 1 and 2 in columns 86-88.	1



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

26 MARCH 1998

Date of mailing of the international search report

15 APR 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

CHANA AULAKH

Telephone No. (703) 308-1235



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/00617

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/00617

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6): A61K 31/18, 31/19, 31/44, 31/47, 31/195, 31/405, 31/415, 31/425, 31/435; C07C 63/00, 307/06, 307/08, 307/10; C07D 213/89, 217/08, 233/44, 233/88, 239/08, 239/42, 209/40

A. CLASSIFICATION OF SUBJECT MATTER:

US CL : 514/275, 303, 310, 352, 357, 365, 371, 396, 398, 415, 563, 603, 613, 616; 544/332; 546/118, 122, 143, 290, 291, 301, 304, 309; 310, 311, 312; 548/195, 300.1, 30 8.4, 335.5, 495; 560/34; 564/86, 147; 568/28

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/275, 303, 310, 352, 357, 365, 371, 396, 398, 415, 563, 603, 613, 616; 544/332; 546/118, 122, 143, 290, 291, 301, 304, 309, 310, 311, 312; 548/195, 300.1, 30 8.4, 335.5, 495; 560/34; 564/86, 147; 568/28

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. The species are as follows:

A. Compounds of claim 1 where Aryl is a 6-membered aromatic ring containing 0 N atoms and Z or A contains N atom, classifiable in class 564, subclass 86+.

B. Compounds of claim 1 where Aryl is a 6-membered aromatic ring containing 0 N atoms and Z or A contains S atom, classifiable in class 568, subclass 18+.

C. Compounds of claim 1 where Aryl is a 6-membered aromatic ring containing 0 N atoms, Y and Z combine to form a carboxylic acid ester, classifiable in class 560, subclass 1+.

D. Compounds of claim 1 where Aryl is a 6-membered aromatic ring containing 1 N atom, classifiable in class 546, subclass 268.1+.

E. Compounds of claim 1 where Aryl is a 6-membered aromatic ring containing 2 N atoms, classifiable in class 544, subclass 224+.

F. Compounds of claim 1 where Aryl is a 6-membered aromatic ring containing 3 N atoms, classifiable in class 544, subclass 180+.

The claims are deemed to correspond to the species listed above in the following manner:

Species A : Claims 3-7

Species D : Claim 3

The following claims are generic: Claims 1, 2 and 8-27

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

There is no common core Which in the Markush Practice, is a significant structural element shared by all the alternatives; see PCT Administrative Instructions Annex B Part I (f) (i) (B) (1) and further, all the alternatives do not belong to a recognized class of chemical compounds to which the invention pertains; see PCT Administrative Instructions Annex B Part I (f) (i) (B) (2).